ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF RACECADOTRIL THROUGH SOLID DISPERSION METHODS

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DEPARTMENT OF PHARMACEUTICS
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CERTIFICATE

This is to certify that the dissertation entitled**, "ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF RACECADOTRIL THROUGH SOLID DISPERSION METHODS."** Submitted by **Mr. V.SELVARAJ** in the Department of Pharmaceutics, Madurai Medical College, Madurai – 20, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by him, under the guidance and supervision of **Prof. Mr.A.Abdul Hasan Sathali**, **M.Pharm.,(Ph.D)** Professor and Head, in the Department of Pharmaceutics, Madurai Medical College, Madurai-20,during the academic year 2011 – 2012.

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I wish him success in all his endeavors.

Place: Madurai

Date: **(Prof. Mr.A.Abdul Hasan Sathali)**

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CONTENTS

CHAPTER-I

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example,parenteral. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal tract (GIT) can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption .Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drug. **(**Lewis S *et al.,* 2009)

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelia and the formulation of poorly soluble drugs for

oral delivery now presents one of the major challenges to formulation scientists in the industries. A review of new monograph (1992-1995) in European pharmacopoeia shows that more than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml.(Aruna Rawat *et al.,*2011).

Most of the newly discovered chemical entities, in spite of high therapeutic activity, have low aqueous solubility and poor bioavailability, leading to poor absorption in the gastrointestinal tracts. For absorption of the drug from the gastrointestinal tracts (GIT), the drug should be present in solution state in GI fluid, which forms a critical requirement for absorption of poorly water-soluble drugs. (Shilpi Sinha *et al.,* 2010)

The solubility of a drug is a key determinant of its oral bioavailability and permeability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol etc., With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. (Anshu Sharma *et al.,* 2011)

Solubility

The term ‘solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms,

solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

Prediction of solubility:

Probably the most sought-after information about solutions in formulation problems is 'what is the best?' or 'what is the worst?' solvent for a given solute. Theoretical prediction of precise solubilities is an involved and occasionally unsuccessful operation, but from knowledge of the structure and properties of solute and solvent an educated guess can be made. This is best expressed in subjective terms, such as 'very soluble' or 'sparingly soluble'. Often (particularly in pre- or early formulation) this is all the information that the formulator requires. The interrelationships between such terms and approximate solubilities are shown in Table. (Aulton M.E et al .,2002)

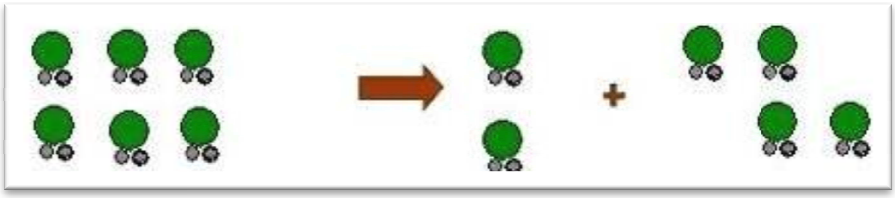
Description	**Approximate weight of solvent (g) necessary to dissolve 1 g of solute**
Very soluble	< 1
Freely soluble	Between 1 and 10
Soluble	Between 10 and 30
Sparingly soluble	Between 30 and 100
Slightly soluble	Between 100 and 1000
Very slightly soluble	Between 1000 and 10 000
Practically insoluble	Above 10 000

PROCESS OF SOLUBILISATION:-

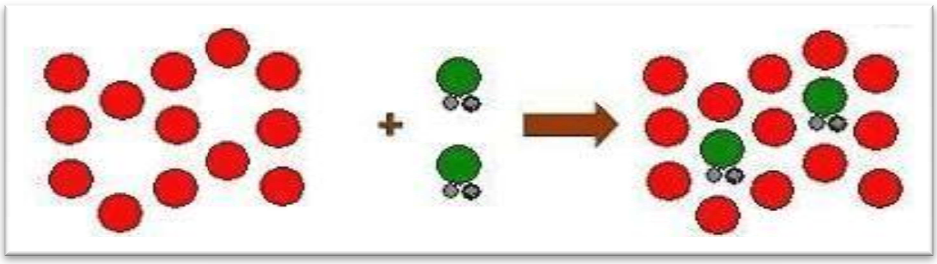
The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion (Harinath N.More *et al.,* 2007).

Step 1: Holes opens in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is intergrated into the hole in the solvent



Possible Causes for Poor Oral Absorption

Any drug is said to be poorly soluble when:

- Aqueous solubility <100µg/ml
- High crystal energy (melting point >200^0 C)
- Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm^2/min,
- High molecular weight: (>500),
- Self association and aggregation.

Noyes-Whitney equation (1) illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

$$dC/dt * h = AD. (Cs - C) \text{ ---------- } (1)$$

Where,

dC/dt is the rate of dissolution,

A is the surface area available for dissolution,

D is the diffusion coefficient of the compound,

Cs is the solubility of the compound in the dissolution medium,

C is the concentration of drug in the medium at time t,

h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

BCS CLASSIFICATION

The BCS was first devised in 1995 by Amidon *et al*. According to the BCS, drug substances can be classified as belonging to one of four classes:

- ✓ Class 1: high solubility and high permeability
- ✓ Class 2: low solubility and high permeability
- ✓ Class 3: high solubility and low permeability
- ✓ Class 4: low solubility and low permeability

Especially for class II substances according to the Biopharmaceutical Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low

gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects.

Class Boundaries Used In BCS:

- A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml water over a pH range 1 to 7.5.
- A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.
- A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of 900 ml buffer solution (Aruna Rawat *et al.,*2011).

FACTORS AFFECTING SOLUBILITY:

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.

Particle Size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles

So is the solubility of fine particles,

V is molar volume,

g is the surface tension of the solid,

r is the radius of the fine particle.

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures.

Molecular size

Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since

more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will

have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

RATE OF SOLUTION:

The rate of solution is a measure of how fast substances dissolve in solvents.

***FACTORS AFFECTING RATE OF SOLUTION*:**

Size of the particles

When the total surface area of the solute particles is increased, the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces increases its surface area and hence its rate of solution.

Temperature

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases, reverse is true.

Amount of solute already dissolved

When there is little solute already in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

Stirring

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution.

TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are:

I. Physical Modifications

A. Particle size reduction

- Micronization
- Nanosuspension

B. Modification of the crystal habit

- Polymorphs
- Pseudopolymorphs

C. Drug dispersion in carriers

- Eutectic mixtures
- Solid dispersions
- Solid solutions

D. Complexation

- Use of complexing agents

E. Solubilization by surfactants:

- Microemulsions
- Self microemulsifying drug delivery systems.

II. Chemical Modifications:-

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material

to a reference standard) of the solvent by the use of co-solvents rather than the pH of the solvent. The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed e.g. Aspirin, Theophylline, Barbiturates. (Harinath N.More *et al.,*2007)

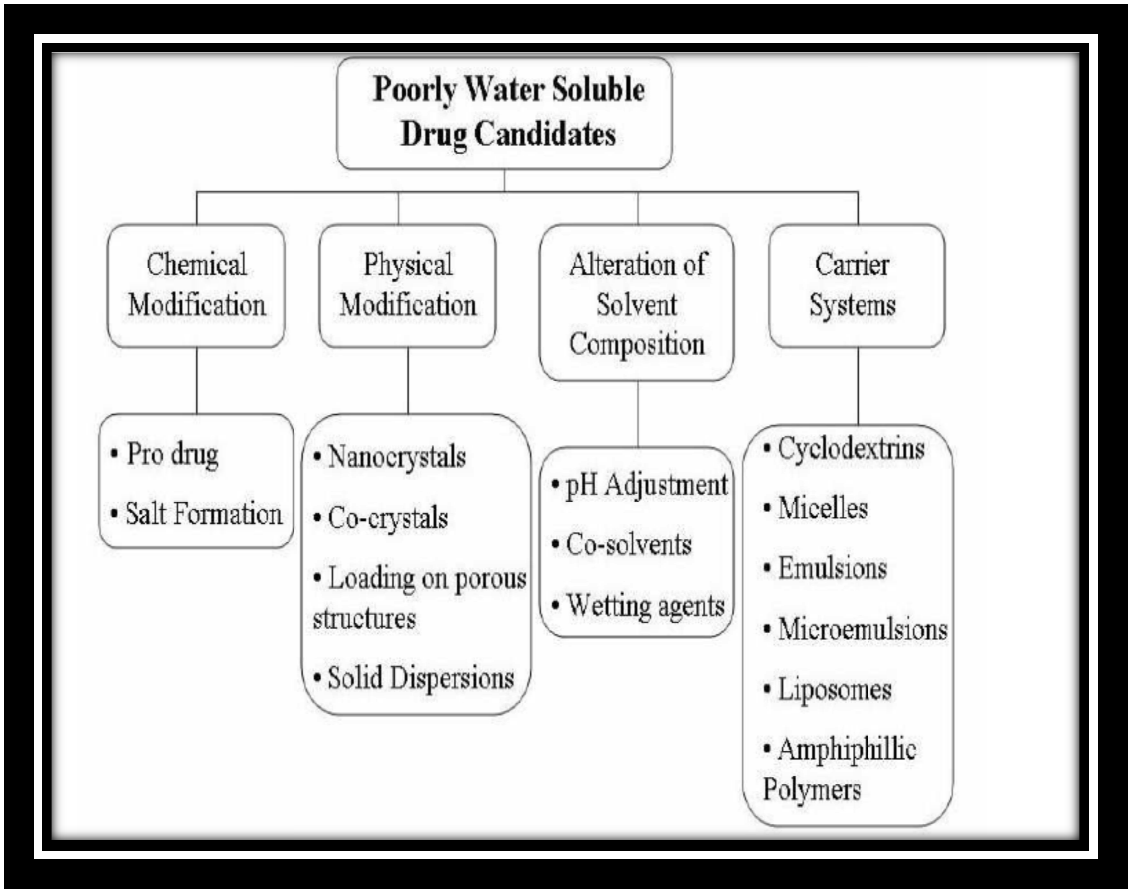
BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG SOLUBILITY OR DISSOLUTION RATE

There are several ways by which drug solubility or the dissolution rate can be enhanced. Some of widely used methods are as follows,

- Micronization
- Nanonisation
- Supercritical fluid recrystallization
- Spray freezing into liquid(SFL)
- Evaporative precipitation into aqueous solution (EPAS)
- Use of surfactants
- Use of salt forms
- Use of precipitation Inhibitors
- Alteration of pH of the Drug Microenvironment
- Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs

- Solvent Deposition
- Precipitation
- Selective Adsorption on Insoluble Carriers
- Solid Solutions
- Eutectic Mixtures
- **Solid dispersions**
- Molecular encapsulation with cyclodextrins.
- Use of solid solutions,

Use of eutectic mixtures and Use of solid dispersions (Brahmankar.D.M, *et al.,* 2009).



CHAPTER-II

SOLID DISPERSION – A REVIEW

Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug (Aruna Rawat *et al*.,2011).

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles (Lewis S *et al*.,2009).

CLASSIFICATION:

***First generation solid dispersions*:**

Description of solid dispersions was given from Sekiguchi and Obi in 1961 showed that formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Later, Levy and Kaning developed solid dispersion. The first systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

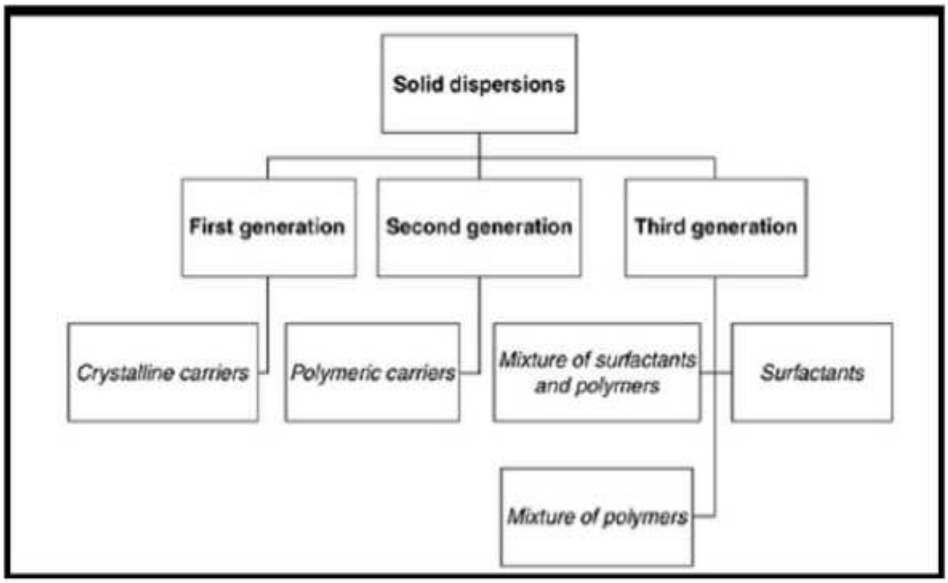
Second generation solid dispersions

It was noticed in the late sixties that Solid dispersion with drug in the crystalline state is not as effective as amorphous because they are thermodynamically stable. Therefore, second generations of solid dispersions were introduced having amorphous

carriers instead of crystalline. Formerly, the drugs were molecularly dispersed in amorphous carriers which are usually polymers in random pattern.

Third generation solid dispersions

Third generation of solid dispersions appeared as the dissolution profile could be increased by using carriers having surface activity and self-emulsifying characteristics. These contain surfactant carriers or a mixture of amorphous polymers and a surfactant as carrier. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug. Surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility (Aruna Rawat *et al*.,2011).



CLASSIFICATION OF SOLID DISPERSION

TYPES OF SOLID DISPERSION

Solid dispersion type		Matrix *	Drug **	Remarks	No. phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1 or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

*A: matrix in the amorphous state, * C: matrix in the crystalline state

**: A: drug dispersed as amorphous clusters in the matrix,

** C: drug dispersed as crystalline particles in the matrix,

M: drug molecularly dispersed throughout the matrix (Lewis S *et al*., 2009).

ADVANTAGEOUS PROPERTIES OF SOLID DISPERSIONS

Particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

Wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions**.** It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

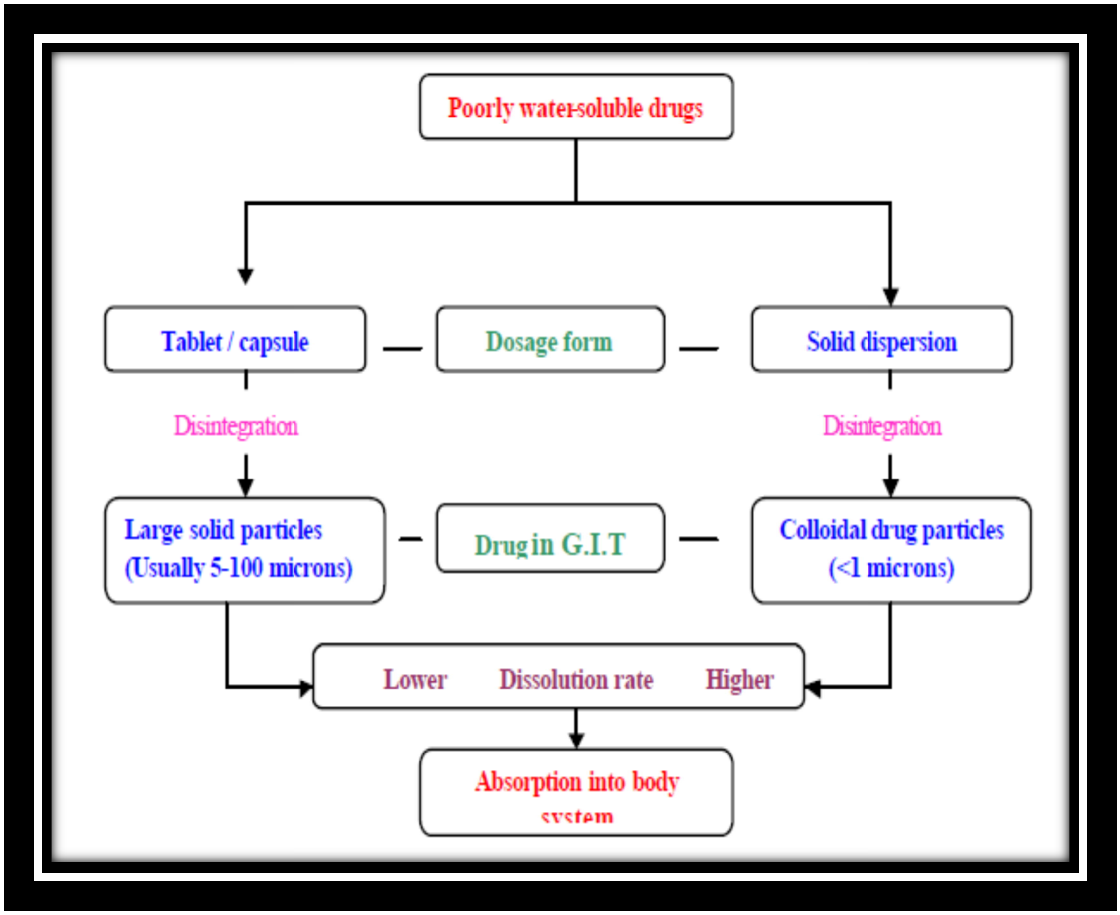
Porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are Presented as

supersaturated solutions after system dissolution and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them. Formulations for enhancing dissolution rate and consequent bioavailability of poorly water-soluble drugs. (Purachikodi *et al*., 2010)



ADVANTAGES OF A SOLID DISPERSION FORMULATION, AS COMPARED TO CONVENTIONAL CAPSULE OR TABLET

PHARMACEUTICAL APPLICATIONS OF SOLID DISPERSION:

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed-

1. To enhance the absorption of drug;
2. To obtain a homogeneous distribution of a small amount of drug in solid state;
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.;
4. To dispense liquid or gaseous compounds;
5. To formulate a fast release priming dose in a sustained release dosage form;
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
7. To reduce side effects-(a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound;
8. To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension;
9. To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc. (Anshu Sharma *et al*.,2011)

DISADVANTAGES:

The limitations of this technology have been a drawback for the commercialization of solid dispersions, the limitations include

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process
5. Stability of the drug and vehicle.

CARRIERS:

The properties of the carrier have the major influence on the dissolution profile of the dispersed drug. A carrier should meet the following criteria to meet to be suit for increasing the dissolution rate of drug.

Selection of a carrier:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Able to preferably increase the aqueous solubility of the drug and
6. Chemically compatible with the drug and not form a strongly bonded complex with the drug.

First generation carriers:

Example: Crystalline carriers: Urea, Sugars and Organic acids.

Second generation carriers:

Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins.

Third generation carriers*:*

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14.

CARRIERS FOR SOLID DISPERSIONS

Sl. No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

SOLVENTS:

Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration (Aruna Rawat *et al*.,2011).

Class I Solvents (Solvents to be avoided):

Solvents included in this class are not to be taken in to use because of their deleterious environmental effects.

List of some Class I Solvents.

Solvent	Concentration limit(ppm)	Effect
Benzene	2	
Carbon tetrachloride	4	Carcinogen Toxic and environmental hazards Toxic
1,2-dichloroethane	5	Toxic
1,1-dichloroethane	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazards

Class II Solvents (Solvents to be limited):

Theses solvent should be limited used in pharmaceutical products because of their inherent toxicity.

Class II solvents in pharmaceutical products

Solvent	PDE(mg/day)	Concentration limit(ppm)
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-dichloroethene	18.7	1870
Ethylene glycol	6.2	620
Methanol	30.0	3000
Pyridine	2.0	200
Toluene	8.9	890

PDE = Permitted daily exposure

Class III Solvents (Solvents with low toxic potential):

Solvents included in this class may be regarded as less toxic and have the low risk to human health.

Class III solvents which should be limited by GMP or other quality based requirement

Acetic acid	Heptane
Acetone	Isobutyl acetate
1-Butanol	Isopropyl acetate
2-Butanol	Methyl acetate
Butyl acetate	3-Methyl-1-Butanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethylacetate	1-Propanol
Ethyl ether	2-Propanol
Formic acid	Propyl acetate

Class IV Solvents (Solvents for which no adequate toxicological data was found):

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example Petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base a PDE was found (Aruna Rawat *et al*.,2011).

METHOD OF PREPARATION:

Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Sekiguchi and obi were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, therefore reducing, the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature, inside a dessicator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a dessicator were used. After cooling, the mixture must be pulverized regarding its handling (Anshu Sharma *et al*.,2011).

***Freeze Drying Method*:**

Drug formulations were processed using ultra-rapid freezing technology. Hydrophilic excipient was dissolved in methanol. Drug, which is poorly water soluble, was added to this separately and dissolved. The resulting ternary system of organic solvent, hydrophilic carrier, and drug was freeze-dried by filling glass vials with the solutions and positioning the vials in a lyophilizer. During operation, the freeze-drier was maintained at -45 °C and a compressional pressure of 0.5 Torr. After complete drying, the vials were taken out, and the dried products were scraped from the vials. The formulations were powdered and packaged in glass vials. (Anjan K. Mahapatra *et al*.,2011)

Solvent Evaporation Method

Tachibana and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65^0 C (Harinath.N More et al.,2007).

Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70 ^{0} C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used (Harinath.N More et al.,2007).

Kneading method

The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1 v/v). The slurry is kneaded for 60 minutes and dried under vaccum for 24 hours. The dried mass is pulverized and sieved through sieve No 60 and stored in a desiccators (Ganesh chaulang *et al*., 2009).

The advantages of this method are low temperature requirement for solid dispersion preparation and usage of organic solvent is less.

Hot melt extrusion

Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer, which broadens the application of hot-stage extrusion to thermally labile compounds. Solid dispersions of Para-amino salicylic acid / Ethylcellulose, Itraconazole / PVP and Itraconazole / Ethylcellulose were successfully prepared by this technique (Anshu Sharma *et al.,*2011).

Spray drying technique

In this technique is one of the most commonly used solvent evaporation procedure in the production of solid dispersions. It consists of dissolving or suspending the carriers, and then spraying it into a stream of heated air flow to remove the solvent (Narasaiah V.L *et al*., 2011).

Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO_2 of most

pharmaceutical compounds is very low (< 0.01wt%) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical (Lewis S *et al*., 2009).

CHARACTERIZATION OF SOLID DISPERSIONS

S.No	Characterization	Methods	Significance
1	Drug-carrier Miscibility	Hot stage microscopy DSC (conventional modulated) pXRD (conventional and variable temp), NMR 1H spin lattice relaxation time	To find out the complex formation between drug and carrier.
2	Drug-carrier interactions	FT-IR spectroscopy Raman spectroscopy Solid state NMR studies	To find out the integration between drug and carrier and formation of inclusion complex.
3	Physical structure	SEM Surface area analysis	To find out the particle size and shape.
4	Surface properties	Dynamic vapor sorption Inverse gas chromatography Atomic force microscopy Raman microscopy	To study the morphology and degree of crystallinity.
5	Amorphous content	Polarized light optical microscopy Hot stage microscopy Humidity stage microscopy DSC (MTDSC), ITC, pXRD	To find out the amorphous from drug.
6	Stability	Humidity studies Isothermal Calorimetry DSC (Tg,temperature recrystallisation) Dynamic vapor sorption Saturated solubility studies	To find out the degree of crystallinity
7	Dissolution enhancement	Dissolution Intrinsic dissolution Dynamic solubility Dissolution in bio-relevant media	To find out the rate and extent ofdissolution

CHALLENGING FUTURES IN SOLID DISPERSION:

Solid dispersion formulations are recently becoming more and more attractive in drug delivery for overcoming poor solubility and bioavailability issues of new drug candidates, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Various issues that impeded the commercial development of solid dispersions include

(a) Inability to scale bench top formulations to manufacturing- sized batches,

(b) Difficulty to control physicochemical properties,

(c) Difficulty in delivering solid dispersion formulations as tablet or capsule dosage forms

(d) Physical and chemical instability of the drug and/or the formulation itself (Purachikodi A *et al*.,2010)

CHAPTER-III

LITERATURE REVIEW

Swain S.K. *et al*., 2011. Design and evaluation of sustained release solid dispersion of Verapamil hydrochloride, with HPMCK4M, Eudragit RSPO by solvent evaporation method. Investigation of the properties of the prepared solid dispersions was performed using release studies and FT-IR. The above research it may be concluded that HPMC K4M acts as a better release retardant for the model drug.

Kalyanwat R *et al*., 2011. Study of enhancement of dissolution rate of carbamazepine by solid dispersion technique. The solid dispersion of carbamazepine was prepared by modified solvent evaporation method. Two types of superdisintegrants croscarmellose sodium & sodium starch glycolate were incorporated. Then prepared different batches of solid dispersion were evaluated by drug content, solubility & dissolution study. Thus dissolution rate of carbamazepine was found to be increasing with superdisintegrant addition.

Raja Rajeswari. K *et al*.,2011. Development, characterization and solubility study of solid dispersion of valsartan. In the present study an attempt was made to improve the solubility and dissolution rate using solid dispersion of a poorly water soluble drug valsartan by using Soluplus as carrier material to enhance the solubility as well as dissolution rate. 5 different formulation were prepared using hot melt extrusion technique in different ratios – 1:1, 1:3,1;5,1:7,1:9. The formulations were further characterized by FT-IR,DSC&SEM analysis. Formulation containing drug: polymer of 1:9 showed the best release with cumulative % drug release of 100 %.

Bobe K.R. *et al* 2011. Formulation and evaluation of solid dispersion of Atorvastatin with carriers like PEG4000, PVP K30, and Mannitol by solvent evaporation and hot melt method. These solid dispersions were analysed for the solubility and invitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate .Further FT-IR, DSC & SEM studies were carried out. Solid dispersion prepared with PEG 6000 shows the presence of amorphous form confirmed by the characterization study.

Bindu Madhavi.B *et al*., 2011 Dissolution enhancement of Efavirenz by solid dispersion and PEGlylation techniques. Solid dispersions were prepared by solvent evaporation and physical mixture method by using PEG. PEGlylated product was also prepared. The prepared products were evaluated for various parameters such as polymer interaction, saturation solubility study and drug release studies .There is an improvement in the dissolution from 10% to 70 % with solid dispersion techniques.

Aswini kumar.G *et al*., 2011 Enhancement of solubility and dissolution rate of Irbesartan by solid dispersion techniques employing various superdisintegrants such as SSG, CP , CCS, MCC. . Solid dispersions were prepared by solvent evaporation and physical mixture method various ratios of drug and carriers were used in the preparation in the ratio of 1:1,1:2, and 1:4. Phase solubility studies of pure drug and solid dispersion was performed. It was found that solubility of irbesartan was increased. The order of increase in dissolution rate with various superdisintegrants CP>SSG>CCS>MMC with irbesartan .FT-IR studies revealed that these was no chemical interaction between drug and carrier when formed as solid dispersion.

Vidyadhara. S *et al*., 2011. Formulation and evaluation of Glimepride solid dispersions and their tablet formulation for enhanced bioavailability. The solid dispersions of Glimeoride with SSG at different ratios were prepared by physical

mixing, solvent evaporation and kneading methods. Among the 3methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of Glimepride.

Chaudhari P.D *et al*.,2011 Solubility enhancement of Etoricoxib by solid dispersion prepared by spray drying technique. The present study was aimed to enhance the solubility and dissolution rate of Etoricoxib by solid dispersions with poloxamer 407 and gelucire 50/13 prepared by spray drying technique. It can be concluded based on the observations of the study that the amorphous form of Etoricocib showed improved biopharmaceutical properties.

Sandeep kumar *et al*.,2011. Effect of non ionic surfactant on the solubility and dissolution of simvastatin. In the present study an attempt has been made to improve the solubility and dissolution of poorly water soluble drug simvastatin using poloxamer 188 as carrier. The kneading technique was used to prepare SD in different ratios In conclusion, solubility and dissolution enhancement of simvastatin was improved by preparing its solid dispersion with poloxamer 188.

Anjan K. Mahapatra *et al*.,2011. Dissolution Enhancement and Physicochemical Characterization of Valsartan in Solid Dispersions with β-CD, HP β-CD, and PVP K-30. Solid dispersions and physical mixtures of valsartan were prepared to increase its solubility characteristics. The drug formulations were characterized in the solid state by FTIR and DSC. By these physical determinations, drug–polymer interactions were found. Both the solubility and the dissolution rate of the drug in these formulations were increased. The FTIR spectroscopic studies show the stability of valsartan and the absence of well-defined drug–polymer interaction. Compared with β-CD, HP β-CD showed better enhancement of dissolution rate;

compared with HP β-CD, PVP K-30 showed better solubility and dissolution enhancement.

Akiladevi.D *et al*., 2011. Preparation And Evaluation Of Paracetamol By Solid Dispersion Technique. The solid dispersion of paracetamol by physical triturating method, and fusion method were prepared using 1:1, 1:4 and 1:5 ratios of drug and polymers (PEG 4000, PEG 6000 and urea) . The solid dispersion was characterized for physical appearance, solubility, IR, and *in vitro* dissolution studies. FTIR study revealed that drug was stable in SDs. Solubility of paracetamol from SDs increased in distilled water. The drug content was found to be high and uniformly distributed in the all formulation. The *in vitro* dissolution studies were carried using USP type XXVII (paddle) type dissolution apparatus. The prepared dispersion showed marked increase in the dissolution rate of paracetamol than that of pure drug.

Dehghan *et al*.,2010. Comparative dissolution study of Glipizide by solid dispersion technique using carriers like PEG 6000, Mannitol by fusion method & PVP K30 by solvent evaporation method. PEG 6000 shows greater solubility and dissolution enhancing capacity than mannitol .

Anshu Sharma *et al*.,2010. Preparation and characterization of solid dispersion of Valsartan with poloxamer 188 by melting method. The solubility of drug increased with increasing polymer concentration. The solid dispersion technique with poloxamer 188 as a carrier provides a promising way to enhance the solubility and dissolution rate of valsaran.

Appa Roa.B *et al*., 2010. Formulation and evaluation of Aceclofenac solid dispersions for dissolution rate enhancement using water soluble carriers like lactose, mannitol and urea by solvent evaporation method. In-vitro release profiles of all solid dispersions were comparatively evaluated and also studied against pure

Aceclofenac. Fast dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose.

Ali Nokhodchi *et al*., 2010. Enhance dissolution rate of poorly water soluble drug carbamazepine using carrier D-Glucosamine Hcl by solvent evaporation method. D-Glucosamine Hcl as a potential hydrophilic carrier to improve dissolution rate of carbamazepine , from physical mixtures and solid dispersions formulations. Different solvents(ethanol,acetone&water) were used as second variable in the preparation of solid dispersions ,physical mixtures of carbamazepine and D-Glucosamine Hcl were also prepared for comparison. The properties of all solid dispersions and physical mixtures were studied using a dissolution test, FT-IR ,SEM and DSC. These results showed that the presence of glucosamine can increase dissolution rate of carbamazepine compared to pure drug.

Gupta Sachin *et al*.,2010. Comparative study of solubility enhancement of poorly soluble drug by solid dispersion and inclusion complex. Famotidine was used as a poorly water soluble drug . The inclusion complex with betacyclodextrin and hydroxy propyl betacyclodextrin have been prepared by different ratios and found that the kneading method shows the better enhancement of solubility in comparison to the solvent evaporation method and physical mixture method. The solid dispersion with PEG 6000 &4000 have been prepared by different ratios and found that solvent evaporation method shows the better enhancement of solubility in comparison to the kneading and physical method. The characterization(FT-IR & SEM) of the complexes shows that the drug shows amorphous form of the complex.

Amit R. Tapas *et al*., 2010. Preparation and characterization of spherically agglomerated solid dispersions by quasi emulsion solvent diffusion method using carriers like PVP K30, HPßCD and HPMC. The pure drug and its agglomerates with different polymers were characterize by DSC, PXRD and SEM. Solid dispersions with different polymers exhibited marked increase in solubility, dissolution rate and micromeritic properties compound with pure drug.

Shilpi Sinha *et al.,* 2010. Solid dispersion as an approach for bioavailability enhancement of poorly water soluble drug Ritonavir. The solid dispersion was prepared using Gelucire as carrier in 1:4 ratio by different method and were characterized for DSC PXRD,SEM & FT-IR. Oral bioavailability of 10mg Ritonavir in solid dispersion prepared by solvent evaporation method and melting method was compared with pure drug after oral administration of solid dispersion and pure drug to albino wistar rats of either sex .In vitro dissolution studies was performed in 0.1N Hcl and bio relevant media showed enhanced dissolution rate as compared to pure drug in both media.

Arun Prasad *et al*., 2010. Preparation and evaluation of solid dispersion of Terbinafine Hcl by melting and solvent evaporation method. Using carriers like PEG6000,PVP K30. The prepared solid dispersions were characterized for their drug content, thermal studies, FT-IR, DSC, Solubility study & dissolution study. From the results, it was clear that solid dispersion formulation showed improved dissolution rate than pure drug & physical mixture.

Prasanthi N.L. *et al*.,2010. Studies on dissolution enhancement of poorly water soluble drug (Lacidipine) with water soluble carriers like PEG6000, 4000, Hydroxy Ethyl Cellulose & Dextrin. The solid dispersions were prepared by solvent evaporation method. Evaluation of the dispersion was performed using dissolution

studies, DSC, FT-IR, & PXRD. The result obtained showed that the rate of dissolution of Lacidipine was considerably improved when formulated in solid dispersions as compare to pure drug.

Patel B *et al*., 2010. Improvement of solubility of cinnarizine by using solid dispersion technique. In the present work solid dispersion of cinnarizine were prepared with a PEG 4000 & PVP K30 by using solvent evaporation & fusion method in the 1:1, 1:2, 1:3 ratio of drug and carrier respectively. Solid dispersion of cinnarizine was evaluated for drug content, FT-IR and in vitro release study. The solid dispersion with PEG & PVP exhibited enhanced dissolution rate of cinnarizine. IR Spectra revealed no chemical incompatibility between drug & carrier.

Kothawade S.N *et al* 2010. Formulation and characterization of Telmisartan solid dispersions. solid dispersions were prepared using PVP , PEG 1500 & 4000 to increase aqueous solubility . Telmisartan solid dispersions were prepared in 1:1, 1:2 & 1:4 ratio of the drug to polymer ratio using solvent evaporation method. The formulations were characterized for solubility parameters, drug content studies, drug release studies and drug – polymer interaction by using FT-IR spectrum. Formulation containing 1:2 ratio of drug: PEG4000 showed the best release as compared to pure drug. The interaction studies showed no interaction between drug and polymer.

Siva Ramakrishna G *et al*.,2010. Enhanced Dissolution Rate Of Ibuprofen By Solid dispersion method. In this study it was shown that the rate of dissolution of poorly soluble drug of ibuprofen was increased by the dispersion of solid dispersions by solvent evaporation and melt method. . In solvent evaporation method the drug was taken with mannitol in the proportions of (1:1, 1:2and 1:3).In solvent evaporation method the rate of dissolution of Ibuprofen was increased with the proportion of (1:3)

when compared to the other formulations. In melt dispersion method the rate of dissolution of Ibuprofen was increased with the proportion of 1:3) when compared to the other formulations. A number of poorly soluble drugs have been shown to improve their dissolution characteristics, when converted to solid dispersion.

Deshmukh D.B. *et al*., 2010. Dissolution Enhancement of Poorly Water Soluble Diacerein by Solid Dispersion technique using PVP K-30 and HPMC E4 as carriers. Four different formulations were prepared by solvent evaporation method with varying drug: carrier ratios viz.1:1, 1:2 1:3 and 1:4 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, DSC, XRD analysis, FTIR spectrum. All the formulations showed marked improvement in the solubility behavior and improved drug release. . The interaction studies showed no interaction between the drug and the carrier.

Tejas Patel *et al*.,2010. Enhancement of dissolution of Fenofibrate by Solid dispersion Technique. Solid dispersions of Fenofibrate were prepared using PEG 6000, Poloxamer 407 and a mixture of PEG 6000 and Poloxamer 407(1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Fenofibrate when dispersed in PEG6000 and Poloxamer 407.

Venkates kumar K *et al*.,2009. Preparation and invitro characterization of valsartan solid dispersions using skimmed milk powder by dispersion method. Four different formulations were prepared with varying drug: lactose viz 1:1,1:2,1:5 and 1:9 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug – polymer

interaction. All the formulations showed marked improvement in the solubility behavior and improved drug release.

Kshirsagar S. J *et al*., 2009. Dissolution improvement of the poorly water soluble drug using dry emulsion and solid dispersion method. The solid dispersions were prepared by solvent evaporation method using HPMCE5LV as water soluble carrier & lactose improve flow properties of solid dispersion. In vitro drug release of solid dispersion was studies by USP Type II (Paddle) dissolution apparatus. Probable mechanisms of improved solubility were characterized by DSC, PXRD and SEM of the drug, Physical mixtures & solid dispersions.

Ganesh chanlang *et al*., 2009. Formulation and evaluation of solid dispersion of Furosemide in sodium starch glycolate by kneading method. Solid dispersion of furosemide in sodium starch glycolate was prepared in ratios of 1:1 and 1:2.In each case, the solid dispersions was characterized by FT-IR , DSC ,PXRD. FT-IR Spectroscopy , DSC &PXRD. Showed a change in crystal structure toward an amorphous form of furosemide .Dissolution data indicated that furosemide dissolution was enhanced.

Yogesh Pore *et al*.,2009. Physicochemical characterization of solid dispersion systems of Tadalafil with Poloxamer 407. Solid dispersion systems of Tadalafil were prepared with Poloxamer 407 in 1:0.5, 1:1.5 and 1:2.5 ratios using the melting method. Characterization of binary systems with FTIR and XRPD studies demonstrated the presence of strong hydrogen bonding interactions, a significant decrease in crystallinity and the possibility of existence of amorphous entities of the drug. In the binary systems tested, 1:0.5 proportion of Tadalafil/Poloxamer 407 showed rapid dissolution of tadalafil.

Tang Xing *et al*.,2008. Nimodipine semisolid capsules containing solid dispersion for improving dissolution. Preparation of a solid dispersion consisting ofNimodipine , Eudragit E100& Plasdone-S630 by hot melt extrusion method. Compared with physical mixture and pure drug ,the dissolution of nimodipine was enhanced dramatically (about 80% within 30 mins) using Powder X Ray Diffraction study, and DSC analysis, both Eudragit E 100 and Plasdone – S630 were found to be compatible with nimodipine in the solid dispersion system.

Nagasamy venkatesh. D *et al*.,2008. Dissolution enhancement of domperidone using water soluble carrier by solid dispersion technique. Solid dispersions of domperidone were prepared using different ratio of PVP K30 as carrier by kneading method. They were evaluated for drug content, intactness of the drug in the formulation and dissolution. IR Spectral and DSC studies were used to characterize the solid dispersion and to study the possibility of complexation of drug with carrier .The dissolution of domperidone from the solid dispersion exhibited higher rates of dissolution and dissolution efficiency values over that of pure drug.

Lynne S. Taylor *et al*.,2008. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine using HPMC acetate succinate, PVP K30 & HPMC 606 by solvent evaporation method. The dissolution behavior of amorphous solid dispersions of felodipine prepared with PVP, HPMC and HPMCAS has been compared. Solid dispersions formulated with HPMCAS were found to result in solutions with the highest extent of supersaturation, whereas HPMC and PVP were less effective. At equivalent supersaturations, all three polymers were observed to reduce crystal growth rates relative to the growth rate of the drug alone. HPMCAS and HPMC were most effective at inhibiting growth rates while PVP was much less effective. These results indicate that it is important to select the appropriate polymer

for a solid dispersion after considering both the solid state stability and the stability of the supersaturated solution generated following dissolution of the amorphous.

Ganesh Chaulang *et al*., 2008. Preparation and Characterization of Solid Dispersion Tablet of Furosemide with Crospovidone 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5oC and 50 rpm in simulated gastric fluid (SGF) of pH 1.2. FTIR spectroscopy, DSC and X-ray diffractometry were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution.

Hoo – Kyun – Choi *et al*., 2006. Preparation of a solid dispersion of Felodipine by solvent wetting method using various polymeric carriers like PVP, HPMC, Poloxamer,Mannitol & sorbitol. The results of DSC & PXRD studies showed that felodipine in solid dispersion exists in the amorphous state in PVP , HPMC and Poloxamer , but not when sorbitol or mannitol used as carriers. The dissolution rate of felodipine from PVP,HPMC &Poloxamer solid dispersions was markedly higher than from their corresponding physical mixtures.

Toshio Ohara *et al*., 2005. Dissolution mechanism of poorly water soluble drug from extended release solid dispersion system with Ethyl cellulose and Hydroxy propyl methyl cellulose. Indomethacin was used as a model of poorly water soluble drug. To investigate the release mechanism of poorly water soluble drug from the extended release solid dispersion system with water insoluble EC and water soluble HPMC (1:1) by suspending method and dissolving method.

Yalcin Ozkan *et al*.,2000. Enhanced release of solid dispersions of Etodolac in polyethylene glycol. Solid dispersions of etodolac were prepared in different molar ratios of drug : carrier by using solvent and melting methods. The release rate of

etodolac from the resulting complexes was determined from dissolution studies by use of USP dissolution apparatus 2 (paddle method). The physical state and drug : PEG interaction of solid dispersions and physical mixtures were characterized by X-ray diffraction (XRD), infrared spectroscopy (IR) and differential scanning calorimetry (DSC). The dissolution rate of etodolac is increased in all of the solid dispersion systems compared to that of the pure drug and physical mixtures. The solid dispersion compound prepared in the molar ratio of 1:5 by the solvent method was found to have the fastest dissolution profile.

Abu T.M Serajuddin *et al*.,2000. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture . Two solid dispersion formulations of the drug, one in Gelucire 44/14® and another one in a mixture of polyethylene glycol 3350 (PEG 3350) with polysorbate 80, were prepared by dissolving the drug in the molten carrier (65 ◦C) and filling the melt in hard gelatin capsules. From the two solid dispersion formulations, the PEG 3350–polysorbate 80 was selected for further development. The oral bioavailability of this formulation in dogs was compared with that of a capsule containing micronized drug blended with lactose and microcrystalline cellulose and a liquid solution in a mixture of PEG 400, polysorbate 80 and water. For intravenous administration, a solution in a mixture of propylene glycol, polysorbate 80 and water was used. Absolute oral bioavailability values from the capsule containing micronized drug, the capsule containing solid dispersion and the oral liquid were 1.7 ± 1.0%, 35.8 ± 5.2% and 59.6 ± 21.4%, respectively. Thus, the solid dispersion provided a 21-fold increase in bioavailability of the drug as compared to the capsule containing micronized drug. A capsule formulation containing 25 mg of drug with a total fill weight of 600 mg was subsequently selected for further development. The selected solid dispersion

formulation was physically and chemically stable under accelerated storage conditions for at least 6 months. It is hypothesized that polysorbate 80 ensures complete release of drug in a metastable finely dispersed state having a large surface area, which facilitates further solubilization by bile acids in the GI tract and the absorption into the enterocytes. Thus, the bioavailability of this poorly water-soluble drug was greatly enhanced by formulation as a solid dispersion in a surface-active carrier

Maria Victoria Margarit *et al*.,1994. Physical characteristic and dissolution kinetics of solid dispersions of Ketoprofen and PEG 6000. To prepare solid dispersions of Ketoprofen and PEG6000 , compared the dissolution kinetics of the solid dispersion with physical mixture and pure drug.Physio-chemical characters were determined by PXRD & DSC. The carrier PEG6000 effectively improves ketoprofen solubilization with 10:90 (drug:polymer) solid dispersion showing best dissolution kinetics.

Valsartan in Solid Dispersions with β-CD,HP β-CD, and PVP K-30. Solid dispersions and physical mixtures of valsartan in β-cyclodextrin , hydroxypropyl β-cyclodextrin , and polyvinyl pyrollidone were prepared to increase its solubility characteristics. The drug formulations were characterized in the solid state by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). By these physical determinations, drug–polymer interactions were found. Both the solubility and the dissolution rate of the drug in these formulations were increased. Drug contents were determined by UV spectrophotometry at a λmax of 249.5 nm.. The SDs of valsartan with β-CD and HP β-CD were prepared at 1:1, 1:3, and 1:5 drug/carrier ratios by a kneading method, and PVP K-30 SDs were prepared at the same ratios (i.e., 1:1, 1:3 and 1:5 drug/carrier) by a lyophilization technique. The FTIR spectroscopic studies show the stability of valsartan and the absence of well-defined drug–polymer interaction. Compared with β-CD, HP β-CD showed better enhancement of dissolution

rate; compared with HP β-CD, PVP K-30 showed better solubility and dissolution enhancement.

CHAPTER-IV

AIM OF THE WORK

The aim of present work, an attempt was made to improve the solubility and dissolution rate of a poorly water soluble drug, Racecodotril.

Racecadotril, also known as acetorphan, is chemically known as Benzyl[[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetate, which is a prodrug of the enkephalinase inhibitor thiophan. It is an antidiarrheal drug which act as a peripherally acting enkephalinase inhibitor**. (**Sasmita kumara acharijya *et al*.,2010) .

Racecadotril, practically insoluble in water, freely soluble in methanol and in methylenechloride (British pharmacopoeia 2009).

Solubility is an important physicochemical factor affecting absorption of drug and it's the therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. Solid dispersions are prepared using PEG 6000, PVP k30 and Poloxamer 188 to increase its aqueous solubility. Racecadotril solid dispersion are prepared in 1:1, 1:2, 1:3 and 1:4 ratios of the drug and carrier ratio (by weight) using kneading, melting, solvent evaporation and freeze drying methods.

CHAPTER-V

PLAN OF WORK

PART I

1. Determination of λ_{max} of Racecadotril
2. Calibration Curve for the drug in Acid buffer P^H 1.2

PART- II

1. Fourier Transform -Infra Red (FT- IR) studies to determine the interaction between carriers with drug.
2. Differential scanning calorimetry (DSC) studies of selected formulations to determine the status of the drug and carrier.

PART-III

1. Formulation of Solid Dispersions of Racecadotril using different ratios of carriers by Melting method, Solvent evaporation method, Kneading method Freeze drying method and physical mixing method.

PART-IV

1. Determination of drug content of all the formulations

PART -V

1. *In-vitro release* profile of the formulated solid dispersions by using acid buffer pH 1.2 as dissolution medium in USP-type-I method (Basket type) at 37^0 C, 100 rpm.

PART-VI

1. Powder X-Ray Diffraction (PXRD) studies of selected formulations (solid dispersion, physical mixture and pure drug) to determine crystallinity of the drug.

2. Solubility studies to determine the solubility of solid dispersion of Racecadotril, physical mixture and pure drug using distilled water and dissolution medium.

CHAPTER-VI

MATERIALS AND EQUIPMENTS

MATERIALS	SUPPLIERS
Racecadotril (Pure drug)	Gift Sample from Safe Tab Life Science Ltd Pondicherry.
PEG 6000	S.D. Fine Chem Ltd - Mumbai
PVP K 30	Nice Chemicals,kochi.
Poloxamer 188	Nice Chemicals,kochi.
Potassium chloride	Central Drug House ,Newdelhi.
Hydrochloric acid	Nice Chemicals,kochi.
Methanol	Astron Chemicals,Ahmedabad.

EQUIPMENTS

EQUIPMENTS	SUPPLIERS
UV-Spectrophotometer	Shimadzu pharma spec UV-1700
Dissolution Apparatus	Labindia - Disso 8000, New Mumbai.
Water Bath	M.C.Dalal & co, Chennai.
Electronic Balance	A & D Company. Japan
Hot Air Oven	Rands Instrument Company, Chennai.
Rotary Flask Shaker	Secor , India
Differential Scanning Colorimeter	DSC 200 TA Instrument , USA
Fourier Transform- Infra Red Spectroscopy	Perkin – Elmer, Germany.
Freeze Dryer	
Powder X Ray Diffractometer	XD, Shimadzu, Japan

CHAPTER-VII

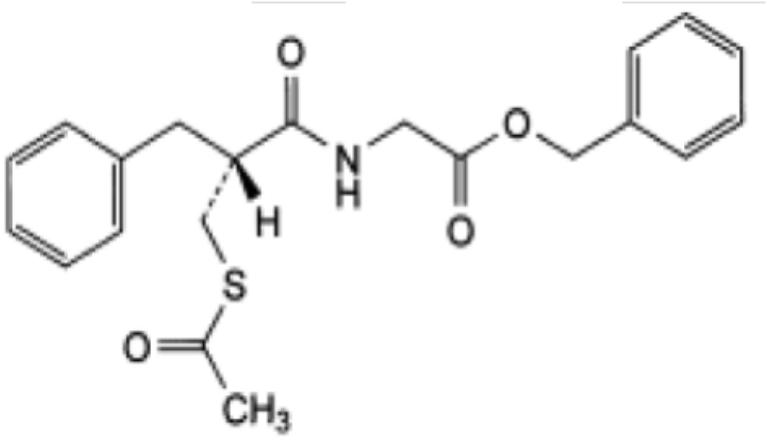
DRUG PROFILE

RACECADOTRIL

SYNONYM:

Acetorphan

STRUCTURE



FORMULA:

$C_{21}H_{23}NO_4S$

MOLECULAR WEIGHT:

385.5

SYSTEMATIC IUPAC NAME:

Benzyl[[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetate

APPEARANCE:

White or almost white powder

SOLUBILITY:

Practically insoluble in water , freely soluble in methanol and in methylene chloride. (British Pharmacopoeia, 2009)

MELTING POINT:

89º c

pka:

13.63

PARTITION COEFFICIENT:

3.44

HALF LIFE:

3 Hours

ROUTE OF ADMINISTRATION:

Oral

DOSE:

100 mg - b.i.d - adult

1.5 mg / kg - children

DOSAGE FORM :

Capsules/ tablets	---	100 mg
DT Tablets	---	10,30 mg
Sachet	---	1g, 1.5g ,3g

USE:

Antidiarrhoeal

PHARMACOLOGY:

Racecadotril is a lipophilic derivative of thiorphan. Racecadotril is rapidly converted in the body to thiorphan,a potent enkephalinase inhibitor.

Enhephalins are endogenous opioid peptides secreted by myenteric and submocosal neurons in the digestive tract.

The enkephalins by activating the opioid receptor , inhibit the secretion of cl- and fluids Thus reducing the loss of fluids and electrolytes during diarrhoea. The antisecretory mechanisms are independent of effects on intestinal motility, differentiating this compound from μ -opiate receptor agonists like loperamide & diphenoxylate.

PHARMACOKINETICS

Racecadotril is administered by the oral route , is well absorbed from the intestinal tract and is rapidly converted to its active metabolite thiorphan. Peak plasma levels are attained in about an hour and half life of the drug is 3 hours.

Data on safety in pregnancy,lactation and renal / hepatic insufficiency is inadequate , which requires care in the usage.

CLINICAL USES

Racecadotril is the first truly intestinal antisecretory drug to treatment of diarrhoea.

ADVERSE EFFECT

Fewer patients on racecadotril therapy suffered from abdominal distension following treatment .

It caused significantly less constipation ,incidence of itching, nausea, vomiting ,thirst, vertigo and head ache.(CIMS)

Racecadotril does not enter the CNS, thus it lacks any potential for neurotoxicity; however in children below 2 years of age where blood brain barrier is immature it can cause depression.(Lt col N.Singh *et al*.,2008**)**

CHAPTER-VIII

EXCIPIENT PROFILE

POLYETHYLENE GLYCOL 6000

(PEG 6000)

SYNONYMS

Carbowax , Carbowax Sentry, Lipoxol, Lutrol E, PEG, Pluriol E , polyoxyethylene glycol

.

CHEMICAL NAME

α-Hydro-ώ-hydroxypoly(oxy-1,2-ethanediyl)

EMPIRICAL FORMULA

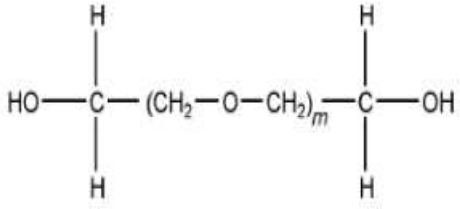
HOCH2 (CH2OCH2) **m**CH2OH

where **m** represents the average of oxyethylene groups

MOLECULAR WEIGHT

6000

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY

Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

DESCRIPTION

Polyethylene glycol grades 200‑600 are liquids , grades 1000 and above are solids at ambient temperatures. Liquid grades occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures. Solid grades are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

TYPICAL PROPERTIES

DENSITY:

1.11‑1.14 g/cm3 at 25 ^{0}C for liquid PEGs

1.15‑1.21 g/cm3 at 25 ^{0}C for solid PEGs.

MELTING POINT:

55-63 ^{0}C for PEG 6000

SOLUBILITY:

All grades of polyethylene glycol are soluble in water . Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

SURFACE TENSION:

Approximately 55mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

VISCOSITY **(** mm^2/s (Cst) at 25^0 C : 580

FREEZING POINT **(** ^{0}**C)** : 56 – 61

PH (5%W/V SOLUTION) : 4.5 – 7.5

RESIDUE ON IGNITION **:** ≤0.25%

HYDROXYL VALUE **:** 16 -22

METHOD OF MANUFACTURE:

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

STORAGE CONDITIONS:

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended

SAFETY

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low. (Raymond C Rowe et al.,2006)

POLOXAMER 188

SYNONYMS

Lutrol, Monolan , Pluronic , poloxalkol , polyethylene‑propylene glycol copolymer, polyoxyethylene‑polyoxypropylene copolymer, Supronic; Synperonic.

CHEMICAL NAME

α-Hydro-ώhydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer

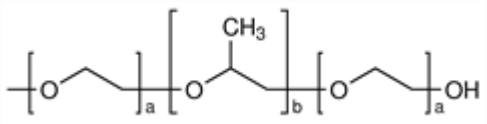
EMPIRICAL FORMULA

$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$.

MOLECULAR WEIGHT

7680 -9510

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY

Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases and gels; and as tablet binders and coatings. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid-dispersion systems.

DESCRIPTION

Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless.

WEIGHT % OXYETHYLENE

81.8 ± 1.9

pH (*aqueous solution* **)***

5 – 7.5

UNSATURATION *(mEq / g* **)**

0.026 ± 0.008

DENSITY

1.06 g /cm^3 at 25 ^{0}c

FLASH POINT

260 ^{0}c

FLOWABILITY

Solid poloxamers are free flowing

HLB VALUE

29

SOLUBILITY

Freely soluble in water and ethanol (95 %)

SURFACE TENSION

19.8mN/m (19.8 dynes/cm) for a 0.1% w/v aqueous poloxamer 188 solution at 25 ^{0}C

VISCOSITY (DYNAMIC)

1000 mPa s (1000 cP) as a melt at 77 ^{0}C for poloxamer 188.

STABILITY AND STORAGE CONDITIONS

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens**.**

METHOD OF MANUFACTURE

Poloxamer polymers are prepared by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol. Ethylene oxide is then added to form the block copolymer**.**

SAFETY

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended (Raymond C Rowe et al.,2006)

POLY VINYL PYROLLIDINE K30

(PVP K30)

SYNONYMS

E1201, Kollidon, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone, povidone , 1-vinyl-2-pyrrolidinonepolymer

CHEMICAL NAME

1-Ethenyl-2-pyrrolidinone homopolymer

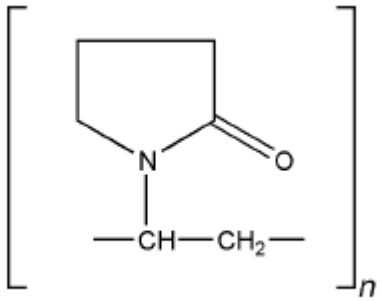
EMPIRICAL FORMULA

(C6H9NO)n

MOLECULAR WEIGHT

50000

STRUCTURAL FORMULA



FUNCTIONAL CATEGORY

Disintegrant; dissolution aid; suspending agent; tablet binder

TYPICAL PROPERTIES

ACIDITY/ALKALINITY: pH = 3.0‑7.0 (5% w/v aqueous solution).

***DENSITY** (bulk):* 0.29‑0.39 g/cm3

***DENSITY** (tapped):* 0.39‑0.54 g/cm3

***DENSITY** (true):* 1.180 g/cm3

FLOWABILITY: 16 g/s for PVP K-29/32.

MELTING POINT: softens at 150 ^{0}C

DYNAMIC VISCOSITY (mpa s)

PVP K-30 3.4 (Ethanol 95 %)
5.8 (Propane -2 – ol)

MOISTURE CONTENT:

povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humudities.

SOLUBILITY:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water, practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

- Carrier for drugs
- Dispersing agent
- Eye drops
- Suspending agent
- Tablet binder, tablet diluent, or coating agent

DESCRIPTION

PVP occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. PVPs with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. PVP K-90 and higher K-value PVPs are manufactured by drum drying and occur as plates.

INCOMPATIBILITIES

PVP is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other

chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with PVP.

METHOD OF MANUFACTURE

PVP is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenatedto butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure.

The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce PVP.

SAFETY

PVP is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, PVP may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. PVP additionally has no irritant effect on the skin and causes no sensitization.

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. (Raymond C Rowe et al.,2006)

CHAPTER-IX

EXPERMENTAL DETAILS

I. CALIBRATION OF RACECADOTRIL

a) Preparation of dissolution medium:

i. Hydrochloric acid buffer pH 1.2:

50 ml of 0.2 M Potassium chloride is placed in a 200 ml volumetric flask. 85 ml of 0.2 M Hydrochloric acid is added and made up to the volume with distilled water. (Indian pharmacopoeia 1996)

ii. 0.2 M Potassium Chloride

14.911 g of Potassium chloride is dissolved with distilled water and the volume is made up to 1000 ml.

iii. *0.2M Hydrochloric acid*

7.292 g of Hydrochloric acid is diluted to 1000 ml with the distilled water.

b) CALIBRATION CURVE OF RACECADOTRIL:

An accurately weighed quantity of 100 mg of Racecadotril pure drug is taken into a clean dried 100ml volumetric flask dissolved in methanol and made upto 100ml with methanol. From this 10ml of the solution is pipette out and volume made upto 100ml with acid buffer solution ph 1.2. From this 5,10,15,20 & 25 ml are pipetted out and diluted to 100ml with acid buffer solution pH 1.2. Absorbance are measured at 232 nm using the acid buffer solution as blank by U-V Spectrophotometer.

II. PREFORMULATION (COMPATABILITY) STUDIES:

a) Differential Scanning Calorimetry (DSC) Studies:

DSC analysis (DSC200 TA instruments,USA) of the samples are carried out on a samples are heated under nitrogen atmosphere on an aluminium pan at a heating rate of 10℃ /min. Over the temperature range 5-200℃. DSC analysis is carried out under nitrogen gas flow of 20 lb/cm^2. (Anshu Sharma *et al*., 2010)

b) Fourier Transform Infra-Red (FT-IR) studies:

While studying the new formulation it is necessary to check the compatibility with the carrier or excipient used and has not undergone degradation. FT-IR spectra (Spectrum RX-1 Perkin-Elmer, German) for the drug and various physical mixtures are obtained in a FT-IR spectroscopy in the transmission mode with the wave number region 4000-400cm^{-1}. KBr pellets are prepared by gently mixing 1mg sample powder with 100mg KBr. (S.K Swain *et al*., 2010)

III. PREPARATION OF SOLID DISPERSION OF RACECADOTRIL

Solid dispersion of Racecadotril is prepared by following methods,

A. Melting method.

B. Kneading method.

C. Solvent evaporation method.

D. Freeze drying method.

E. Preparation of physical mixture

A) MELTING METHOD

Water soluble carriers (PEG 6000 & Poloxamer 188) are taken in a china dish and heated at 60ºc in a water bath, until the mixture melts completely. The drug (Racecadotril) is added to the molten polymer and mixed thoroughly. The dispersion is cooled to ambient condition. Solidified mass is crushed, pulverized and passed through sieve no 120, and stored in a desiccator. (Anshu Sharma *et al.,* 2010)

B) KNEADING METHOD

A mixture of drug (Racecadotril) and carriers (PEG 6000, PVP K30 & Poloxamer 188) in different ratio (1:1,1:2,1:3,1:4) are wetted with solvent (methanol) and water (1:1 ratio) , and kneaded thoroughly for 30 minutes in a glass mortar**.** The paste formed is dried under vacuum for 24 hours. Dried powder is scrapped, crushed, pulverized and passed through sieve no 120 and stored in desiccator. (D.Nagasamy venkatesh *et al*., 2008)

C) SOLVENT EVAPORATION METHOD

Racecadotril solid dispersions are prepared by solvent evaporation method using carrier PVP K30 in proportions viz., (1:1, 1:2, 1:3, and 1:4).The drug and carrier are dissolved in methanol in a china dish and the mixture is heated until the solvent evaporated and clear film of drug and carrier is obtained. The resultant solid dispersion is scraped out with a spatula .Dispersions are pulverized in a mortar and pestle and passed through a 125µm sieve before packing in an airtight container**.**(Kothawade S.N *et al*., 2010)

D) FREEZE DRYING METHOD

Hydrophilic carrier (PVP K30) is dissolved in organic solvent, poorly water soluble drug (Racecadotril) is added to this separately and dissolved. The resulting ternary system of organic solvent, hydrophilic carrier and drug is freeze dried by filling glass vials with the solutions and positioning the vials in a lyophilizer. During operation, the freeze dried is maintained at -45 c and a compressional pressure of 0.5 torr. After complete drying, the vials are taken out, and the dried products are scraped from the vials. The formulations are powdered and packaged in glass vials. (Anjan K. Mahapatral *et al*., 2008)

E) PREPARATION OF PHYSICAL MIXTURE

The physical mixture is prepared by mixing of drug and carrier in a glass mortar. Solid mass is pulverized and passed through sieve no 120 to get uniform sized particles. (Venkatesh Kumar. K *et al*., 2009)

IV. CHARACTERIZATION OF SOLID DISPERSION

a) Estimation of drug content
b) *In-vitro* dissolution studies
c) Solubility studies
d) Powder *X- ray* diffraction studies (PXRD)

a) *Estimation of Drug Content*

Physical mixtures and solid dispersions equivalent to 10mg of racecadotril are weighed accurately and dissolved in 10ml of methanol. The

solution is filtered, diluted suitably with acid buffer ph 1.2 and drug content is analyzed at 232 nm by UV –Spectrophotometer. (Appa Rao. B *et al*., 2010)

$$\% \ drug\ content = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

b) ***In-vitro*** **Dissolution Studies**

Dissolution study is carried out by using USP rotating basket (Apparatus-I) for 1 hour, the stirring rate is 100rpm. Acid buffer pH 1.2 is used as dissolution medium (900ml) and temperature is maintained at 37± 0.5℃. Samples equivalent to 100mg of racecadotril is filled in hard gelatin capsules used for dissolution studies. Samples are collected at regular interval of time (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60min). The absorbance of the samples is measured at ƛ max 232 nm after suitable dilution using appropriate blank**.** (Dehghan M H G *et al.*, 2010)

c) Solubility Studies:

Solubility study is assessed out according to the method of Higuchi and Cannors. The solubility of racecadotril as pure drug, physical mixture and solid dispersion (KM 7) are determined in distilled water and acid buffer PH 1.2. Samples are equivalent to 10mg of drug is taken and to this 10ml of respective medium is being added in 250ml conical flask, and shaken for 24 hours at room temperature on Rotary Flask Shaker. The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples are filtered through whatman filter paper and aliquots are suitably diluted and assayed by spectrophotometrically at 232nm.(Dehghan *et al*.,2010)

d) Powder X Ray Diffraction Studies (PXRD)

Powder X-ray diffraction patterns (XRD) of the pure drug, physical mixture (PM7) and solid dispersion (KM7) were monitored with an X-Ray Diffractometer (XD, Shimadzu, Japan) using copper as x-ray target, a voltage of 40 KV, a current of 30 mA and with 1.5404 Angstrom wavelength. The samples were analyzed over 2θ range of 7.02-59.980 with scanning step size of 0.020 (2θ) and scan step time of one second.(Amit R Tapas *et al*.,2010).

CHAPTER-X

RESULTS AND DISCUSSION

I. CALIBRATION OF RACECADOTRIL

The λmax of Racecadotril was determined by scanning the 10µg/ml of the drug solution in acid buffer solution pH 1.2. It showed the λ max of 232 nm in methanol and acid buffer solution pH1.2(Fig 1-A). Linear correlation coefficient was obtained (r^2 = 0.9993) for calibration of Racecadotril (Fig 1-B). (A. Laksmana Rao *et al*., 2010)

Racecadotril obeys the Beer's law within the concentration range of 5-25 µg/ml. (Table- 3)

II. PREFORMULATION (COMPATABILITY) STUDIES:

a) Differential Scanning Colorimetry (DSC) Studies

The DSC thermograms of Racecadotril and of its physical mixtures are shown in Fig 34-40 . The sharp melting point peak of pure racecadotril appeared at 80.9^{0}C, whereas no such peak was observed in physical mixtures (1:1) prepared with PEG6000, PVP K30 and Poloxamer 188, suggesting that racecadotril was molecularly dispersed and in an amorphous form.(Fig 34-40). **(**Hoo-Kyun choi *et al*., 2006).

b) Fourier Transform Infra-Red (FT- IR) Studies

The FT-IR Spectra of Racecadotril and its binary systems with PVP K30, PEG6000 and Poloxamer 188 are present in Fig 27-33. Pure racecadotril spectra showed sharp characteristic peaks at 3939.91, 3285.52, 1950.86, 1644.82, 1289.86, 695.30 $cm^{-1.}$. All the above characteristic peaks appear in the spectra of all binary

systems are within the same wave number indicating no modification or interaction between drug and carrier. (Patel B *et al*., 2010)

III. PREPARATION OF RACECADOTRIL SOLID DISPERSIONS:

In the present study, 28 formulations of Racecadotril solid dispersions were prepared by using water soluble carriers like PEG6000, Poloxamer 188 and PVP K30, in the ratio of 1:1,1:2.1:3 and 1:4 in 4methods (Melting method, Kneading method, Solvent evaporation method and Freeze drying method) (Table-4) .The prepared solid dispersions were found to be uniform and homogeneous in appearance.

PEG6000 and Poloxamer 188 were used in the preparation of both melting and kneading method (16 formulations), but PVP K30 used in the preparation of kneading method, solvent evaporation method and freeze drying method (12 formulations), because of its hygroscopic nature. (Anjan K. Mahapatra *et al*., 2011)

IV. CHARACTERIZATION OF SOLID DISPERSION

a) Estimation of Drug Content:

The drug content in all the formulations was estimated spectrophotometrically at 232 nm (Shimadzu UV1700, Pharmspec, Japan). The drug content of the prepared solid dispersions was found to be in the range of 95 % to 101.3% indicating the uniform distribution of drug in the formulation. (Table -1) (Kumar Sandeep *et al.,* 2011)

b) In-vitro Release Studies:

The In vitro dissolution studies of Racecadotril from solid dispersions were performed by using USP Type I (Basket) dissolution apparatus in 900 ml of acid buffer pH1.2 at 37^0 C± 0.5^0 C at 100 rpm.10ml of samples were withdrawn regular

intervals of 5 minutes for 1 hour and the same volume of fresh dissolution medium was replaced after every withdrawal. The withdrawn samples were diluted suitably and analyzed by UV- visible spectrophotometer at 232 nm. (Ganesh Chaulang *et al*., 2009)

The cumulative percentage drug release profile data obtained for all solid dispersion formulations are tabulated in Table no 5 to 14.

In kneading method, 3 different carriers were used. The release profiles of PEG6000,in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 44.4% (KM1), 56.5%(KM2), 45.3%(KM3), 47.9 %(KM4) after 1 hour (Fig -3).From the results, it was observed that KM2(1:2 ratio) exhibits maximum release of 56.5% and it was rated as the best formulation in kneading method using PEG6000. In case of PVP K30, in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 46.4%(KM5), 43.7%(KM6), 72.7%(KM7), 52%(KM8) after 1 hour(Fig- 4) . From the results, it was observed that KM7(1:3 ratio) exhibits maximum release of 72.7% and it was rated as the best formulation in kneading method using PVP K30.The release profile of Poloxamer 188 in the ratios of 1:1 ,1:2, 1:3, 1:4 were found to be 57.5%(KM9), 57.3%(KM0), 57.8%(KM11), 53.1 %(KM12) after 1 hour (Fig -5). From the results, it was observed that KM11(1:3 ratio) exhibits maximum release of 57.8% and it was rated as the best formulation in kneading method using Poloxamer 188.

In melting method, two different carriers were used. The release profiles of PEG6000, in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 55.8%(MM1), 59.7%(MM2), 57.7%(MM3), 46.6%(MM4) after 1 hour (Fig -6). From the results, it was observed that MM2(1:2 ratio) exhibits maximum release of 59.7% and it was rated as the best formulation in melting method using PEG6000. In case of

Poloxamer188, in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 55.8%(MM5), 52.5%(MM6), 51.3%(MM7), 50.7%(MM8) after 1 hour (Fig -7) . From the results, it was observed that MM5(1:1 ratio) exhibits maximum release of 55.8% and it was rated as the best formulation in melting method using Poloxamer 188.

In Freeze drying method, PVP K30 was used as a carrier. The release profiles of PVP K30 ,in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 47.4%(FD1), 56%(FD2), 60.6%(FD3), 58.2%(FD4) after 1 hour (Fig -23). From the results it was observed that the release profile of FD3(1:3 ratio) is higher than the release profiles of other formulations in this method.

In Solvent evaporation method, PVP K30 was used as a carrier. The release profiles of PVP K30 ,in the ratios of 1:1, 1:2, 1:3, 1:4 were found to be 69.4%(SEM1), 54.2%(SEM2), 63.2%(SEM3), 51.3%(SEM3) after 1 hour (Fig -24) . From the results it was observed that the release profile of SEM1(1:1 ratio) is higher than the release profiles of other formulations in this method.

In 1:1 ratio, the solid dispersion prepared by using PVP K30 employing solvent evaporation method, was found to be the best with the release rate of 69.4%(SEM1) at 1 hour (Fig-11,15,19), compared with the release profile of 44.4%(KM1), 46.4%(KM5), 57.5%(KM9), 55.8%(MM1 & MM5), 47.4%(FD1), 31.5%(PM1), 43.1%(PM5), 47.8%(PM9). From the results it was observed that the release profile of SEM1 is higher than the release profiles of other formulations in this ratio.

In 1:2 ratio, the solid dispersion prepared by using PEG6000 employing melting method, was found to be the best with the release rate of 59.7%(MM2) at 1 hour (Fig-12,16,20), compared with the release profile of 56.5%(KM2), 43.7%(KM6),

57.3%(KM10), 52.5%(MM6), 56%(FD2), 54.2%(SEM2), 30.6%(PM2), 38.7%(PM6), 52.3%(PM10). From the results it was observed that the release profile of MM2 is higher than the release profiles of other formulations in this ratio.

In 1:3 ratio, the solid dispersion prepared by using PVP K30 employing kneading method, was found to be the best with the release rate of 72.7%(KM7) at 1 hour (Fig-13,17,21), compared with the release profile of 45.3%(KM3), 57.8%(KM11), 57.7%(MM3), 51.3%(MM7), 60.6%(FD3), 63.2%(SEM3), 42.4%(PM3), 40%(PM7), 52.2%(PM11). From the results it was observed that the release profile of KM7 is higher than the release profiles of other formulations in this ratio.

In 1:4 ratio, the solid dispersion prepared by using PVP K30 employing freeze drying method, was found to be the best with the release rate of 58.2%(FD4) at 1 hour (Fig-14,18,22), compared with the release profile of 47.9%(KM4), 52%(KM8), 53.1%(KM12), 46.6%(MM4), 50.7%(MM8), 51.3%(SEM4), 45.9%(PM4), 37.5%(PM8), 51.1%(PM12). From the results it was observed that the release profile of FD4 is higher than the release profiles of other formulations in this ratio.

In vitro release studies reveal that there is marked increase in the dissolution rate of racecadotril from all the solid dispersions when compared to physical mixture and pure drug.

From the in vitro drug release profile, it can be seen that formulation KM 7(Kneading method) containing PVP K30 (1:3 ratio of drug: carrier) showed higher dissolution rate 72.7% after 1hour, and so it was considered as the overall best formulation.

The solid dispersion of Racecadotril was prepared by three different carriers namely PEG6000, PVP K30, Poloxamer 188, employing various techniques. From the result it was observed that, among the 3 carriers, PVP K30 was found to have greater released rate than other two carriers.

PVP K30 > Poloxamer 188 > PEG 6000

The increase in dissolution of the drug in both, the physical mixtures and solid dispersions was reported because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug in the formulations. **(**Chaudhari P.D *et al*., 2011)

But as the amount of PEG6000, PVP K30 and Poloxamer 188 were increased (1:4 ratio) in all formulation, the dissolution rate was decreased .This decrease in dissolution rate may be due to increased viscosity of coating materials. (Kothawade.S**.** *et al*., 2010)

Drug release from the solid dispersion formulation (KM 7) was found to be significantly higher as compared with that of marketed Racecadotril capsules. (Gupta *et al*., 2011) **(**Table – 16) (Fig- 25)

c) Solubility Studies:

The solubility study was conducted with pure drug, physical mixture and solid dispersion (KM 7) using distilled water and acid buffer pH 1.2 shown in Table no 15. It was observed that the solid dispersion (0.344 mg/ml) (KM 7) has highest solubility compared to pure drug (0.103 mg/ml) and physical mixture (0.161 mg/ml) (PM7) in both distilled water and acid buffer pH 1.2. (Fig -26) (Dehghan *et al.*, 2010**)**

d) Powder X Ray Diffraction (PXRD) Studies:

The Powder X-Ray Diffraction patterns of solid dispersion of racecadotril (KM7) with the physical mixture (PM7) and pure drug shown in Fig 41-43. In the case of solid dispersion of racecadotril with PVP K30, no characteristic racecadotril peaks were observed. These results are confirmed that racecodotril was transferred from a crystal to an amorphous form upon dispersion by the kneading method. (Hoo-Kyun Choi *et al*.,2006).

TABLE -1 PERCENTAGE DRUG CONTENT

S.NO	FORMULATION CODE	% DRUG CONTENT AVERAGE ±SD
1.	KM 1	95.3 ± 2.72
2.	KM 2	95 ± 2.40
3.	KM 3	95.5 ± 3.31
4.	KM 4	98.8 ± 3.67
5.	KM 5	96.6 ± 1.40
6.	KM 6	96.4 ± 1.04
7.	KM 7	95.2± 2.00
8.	KM 8	96.1± 0.37
9.	KM 9	97± 2.33
10.	KM 10	99.9± 4.83
11.	KM 11	98.5± 0.75
12.	KM 12	96.6± 0.99
13.	MM 1	101.3± 1.68
14.	MM 2	98.6± 1.68
15.	MM 3	97.8± 2.14
16.	MM 4	98.3± 5.80
17.	MM 5	95.8± 1.40
18.	MM 6	97.5± 1.30
19.	MM 7	96.1± 2.72
20.	MM 8	98.5± 2.72
21.	FD 1	100.5± 1.68
22.	FD 2	101.3± 3.69
23.	FD 3	96.4± 3.17
24.	FD 4	99.9± 2.89
25.	SEM 1	97.2± 0.99
26.	SEM 2	99.4± 1.04
27.	SEM 3	99.6± 1.40
28.	SEM 4	99.9± 1.34

29.	PM 1	96.5± 1.39
30.	PM 2	95.3± 1.04
31.	PM 3	98.6± 2.14
32.	PM 4	96.4± 1.04
33.	PM 5	100.2± 2.04
34.	PM 6	99.4± 1.04
35.	PM 7	98.8± 2.04
36.	PM 8	98.3± 1.77
37.	PM 9	100.2± 1.03
38.	PM 10	98± 0.37
39.	PM 11	96.2± 2.40
40.	PM 12	95.3± 1.40

TABLE - 2 PERCENTAGE YIELD

S.NO	FORMULATION CODE	% YIELD
1.	KM 1	97.2
2.	KM 2	98.5
3.	KM 3	98.6
4.	KM 4	99.1
5.	KM 5	98.7
6.	KM 6	98.4
7.	KM 7	98.8
8.	KM 8	85.6
9.	KM 9	97.5
10.	KM 10	85.4
11.	KM 11	84.8
12.	KM 12	99.3
13.	MM 1	96.8
14.	MM 2	94.4
15.	MM 3	95.1
16.	MM 4	99.1
17.	MM 5	91.8
18.	MM 6	98.9
19.	MM 7	94.6
20.	MM 8	87.5
21.	FD 1	89.8
22.	FD 2	87.3
23.	FD 3	91.2

24.	FD 4	90.4
25.	SEM 1	93.6
26.	SEM 2	95.7
27.	SEM 3	89.5
28.	SEM 4	87.9
29.	PM 1	99
30.	PM 2	99.5
31.	PM 3	99.6
32.	PM 4	99.6
33.	PM 5	99.5
34.	PM 6	99.4
35.	PM 7	99.6
36.	PM 8	99.7
37.	PM 9	99.2
38.	PM 10	99.5
39.	PM 11	99.5
40.	PM 12	99.6

TABLE – 3 CALIBRATION OF RACECADOTRIL (pH 1.2)

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE at 232 nm (Avg ± SD)
1	5	0.061±0.0016
2	10	0.122±0.0016
3	15	0.189±0.0016
4	20	0.260±0.0016
5	25	0.334±0.0020

REGRESSION (R^2) = 0.9993

TABLE – 4 FORMULATION CHART

S.NO	FORMULATION CODE	COMPOSITION	RATIO	METHOD
1.	KM 1	DRUG : PEG 6000	1:1	KNEADING
2.	KM 2	DRUG : PEG 6000	1:2	KNEADING
3.	KM 3	DRUG : PEG 6000	1:3	KNEADING
4.	KM 4	DRUG : PEG 6000	1:4	KNEADING
5.	KM 5	DRUG : PVP K30	1:1	KNEADING
6.	KM 6	DRUG : PVP K30	1:2	KNEADING
7.	KM 7	DRUG : PVP K30	1:3	KNEADING
8.	KM 8	DRUG : PVP K30	1:4	KNEADING
9.	KM 9	DRUG : POLOXAMER 188	1:1	KNEADING
10.	KM 10	DRUG : POLOXAMER 188	1:2	KNEADING
11.	KM 11	DRUG : POLOXAMER 188	1:3	KNEADING
12.	KM 12	DRUG : POLOXAMER 188	1:4	KNEADING
13.	MM 1	DRUG : PEG 6000	1:1	MELTING
14.	MM 2	DRUG : PEG 6000	1:2	MELTING
15.	MM 3	DRUG : PEG 6000	1:3	MELTING
16.	MM 4	DRUG : PEG 6000	1:4	MELTING
17.	MM 5	DRUG : POLOXAMER 188	1:1	MELTING
18.	MM 6	DRUG : POLOXAMER 188	1:2	MELTING
19.	MM 7	DRUG : POLOXAMER 188	1:3	MELTING
20.	MM 8	DRUG : POLOXAMER 188	1:4	MELTING
21.	FD 1	DRUG : PVP K30	1:1	FREEZE DRYING
22.	FD 2	DRUG : PVP K30	1:2	FREEZE DRYING

23.	FD 3	DRUG : PVP K30	1:3	FREEZE DRYING
24.	FD 4	DRUG : PVP K30	1:4	FREEZE DRYING
25.	SEM 1	DRUG : PVP K30	1:1	SOLVENT EVAPORATION
26.	SEM 2	DRUG : PVP K30	1:2	SOLVENT EVAPORATION
27.	SEM 3	DRUG : PVP K30	1:3	SOLVENT EVAPORATION
28.	SEM 4	DRUG : PVP K30	1:4	SOLVENT EVAPORATION
29.	PM 1	DRUG : PEG 6000	1:1	GRINDING
30.	PM 2	DRUG : PEG 6000	1:2	GRINDING
31.	PM 3	DRUG : PEG 6000	1:3	GRINDING
32.	PM 4	DRUG : PEG 6000	1:4	GRINDING
33.	PM 5	DRUG : PVP K30	1:1	GRINDING
34.	PM 6	DRUG : PVP K30	1:2	GRINDING
35.	PM 7	DRUG : PVP K30	1:3	GRINDING
36.	PM 8	DRUG : PVP K30	1:4	GRINDING
37.	PM 9	DRUG : POLOXAMER 188	1:1	GRINDING
38.	PM 10	DRUG : POLOXAMER 188	1:2	GRINDING
39.	PM 11	DRUG : POLOXAMER 188	1:3	GRINDING
40.	PM 12	DRUG : POLOXAMER 188	1:4	GRINDING

TABLE - 5 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PEG 6000 BY KEADING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*				
	PURE DRUG	KM 1 (1:1)	KM 2(1:2)	KM 3(1:3)	KM 4(1:4)
5	5.6±4.90	16.6±1.11	8.85±0.35	11.8±1.06	13.5±0.61
10	9.4±0.37	18.7±0.61	13.1±0.57	15.6±1.14	17.2±0.94
15	11.5±1.06	21.6±0.65	20.4±0.61	19.1±1.39	23.7±1.11
20	12.9±1.02	23.4±0.82	25.2±0.38	26.7±5.91	26.4±1.35
25	15.3±0.98	25.1±1.67	38.4±1.39	32.1±3.55	35.5±0.82
30	18.5±0.32	26.7±1.97	44.3±0.77	35.1±2.06	37.6±0.87
35	22.5±0.60	29.6±2.37	46.9±0.49	36.7±2.08	39.8±0.98
40	24.9±0.43	32.6±2.93	51.2±0.37	37.6±2.26	40.8±1.14
45	25.6±0.70	34.9±2.93	54.8±0.35	39.7±2.05	42.6±0.61
50	26.1±0.43	38.3±3.20	54.7±0.74	41.9±1.26	44.8±0.86
55	27.4±0.05	41.6±2.14	55.7±0.49	43.7±1.31	46.6±0.90
60	28.1±0.32	44.4±1.55	56.5±0.35	45.3±0.96	47.9±1.01

TABLE-6 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY KEADING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	KM 5(1:1)	KM 6(1:2)	KM 7(1:3)	KM 8(1:4)
5	11.7 ± 0.53	13.5± 0.83	9.6 ± 0.61	13.3 ± 0.82
10	15 ± 0.82	15.8 ± 0.53	13.4 ± 0.82	16.3 ± 0.82
15	19.7 ± 1.35	18.7 ± 1.63	18.4 ± 0.63	22.6 ± 1.02
20	22.3 ± 0.30	22.2 ± 1.63	23 ± 0.82	29.2 ± 0.79
25	24.1 ± 0.79	24.6 ± 0.82	48.8 ± 1.74	36.4 ± 1.06
30	28.6 ± 1.83	27.5 ± 0.35	53.6± 0.53	43.7 ± 0.59
35	31.5 ± 1.63	30 ± 0.88	56.3 ± 0.53	49.9 ± 0.83
40	34.7 ± 2.79	32.9 ± 0.82	60.4± 0.83	51.7 ± 0.70
45	37.7 ± 3.36	36.3 ± 0.61	64.4 ± 0.83	51.5 ± 0.57
50	40.9 ± 2.30	38.5 ± 0.49	67.3 ± 0.35	51.8 ± 0.82
55	44.2 ± 1.18	40.8 ± 0.57	70 ± 0.63	52.3 ± 0.83
60	46.4 ± 0.91	43.7 ± 0.63	72.7 ± 0.35	52± 0.82

TABLE -7 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 BY KEADING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	KM 9	KM 10	KM 11	KM 12
5	11.1 ± 0.53	14.8 ± 0.79	11.1 ± 0.53	14 ± 0.82
10	19.8 ± 1.43	20.3 ± 0.28	13.8 ± 0.53	16.7 ± 1.14
15	28.1 ± 1.35	25.7 ± 1.66	20.2 ± 0.82	20.9 ± 0.82
20	31.7 ± 0.32	29.5 ± 0.94	27.2 ± 0.63	25.5 ± 1.88
25	36.7 ± 1.15	35.8 ± 1.06	34.3 ± 0.57	31.9 ± 2.69
30	45.4 ± 3.36	39.9 ± 1.74	41.9 ± 0.57	38.4 ± 4.01
35	50.7 ± 1.96	45.1 ± 0.61	48.2 ± 0.53	43.2 ± 4.12
40	55.2 ± 0.41	49.2 ± 0.35	50.1 ± 0.57	49.4 ± 2.40
45	57.1 ± 0.73	51.7 ± 0.37	52.2 ± 0.35	52.9 ± 1.26
50	56.6 ± 0.69	55 ± 0.59	54.2 ± 0.65	53.3 ± 1.16
55	56.1 ± 0.50	57.8 ± 0.57	55.9 ± 0.87	53.4 ± 1.47
60	57.5 ± 0.54	57.3 ± 0.26	57.8 ± 0.32	53.1± 0.47

TABLE - 8 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PEG 6000 BY MELTING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	MM 1(1:1)	MM 2(1:2)	MM 3(1:3)	MM 4(1:4)
5	8.7 ± 0.32	10 ± 0.40	12 ± 0.34	12.4 ± 0.53
10	15.3 ± 0.86	13.8 ± 0.65	14.8 ± 1.01	20.6 ± 0.61
	19.7 ± 0.35	19.5 ± 0.34	18.6 ± 0.65	23.3 ± 0.53
20	24.9 ± 0.65	21 ± 0.97	24.1 ± 0.65	31.7 ± 0.82
25	30.9 ± 0.53	24.8 ± 1.01	30.1 ± 1.78	36.2 ± 0.82
30	35.8 ± 0.61	30.9 ± 0.88	35.9 ± 0.65	37.9 ± 0.61
35	40.9 ± 0.53	36.1 ± 0.65	40.4 ± 0.40	41.2 ± 1.43
40	49.2 ± 0.53	43.2 ± 2.26	45 ± 1.02	45.1 ± 1.62
45	54.1 ± 0.77	49 ± 0.91	49.2 ± 0.37	45.6 ± 0.82
50	54.9 ± 0.49	54.1 ± 0.37	51.5 ± 0.65	46.5 ± 0.00
55	54.9 ± 0.44	56.7 ± 0.34	54.7 ± 1.75	46.3 ± 0.04
60	55.8 ± 0.54	59.7 ± 0.65	57.7 ± 1.08	46.6± 0.61

TABLE – 9 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 BY MELTING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	MM 5(1:1)	MM 6(1:2)	MM 7(1:3)	MM 8(1:4)
5	8.7 ±0.32	9.4 ±0.82	8.7 ±0.32	8.7 ±0.32
10	16.9 ±0.30	13.4 ±0.80	16 ±2.60	11.6 ± 0.30
15	21.9 ±0.53	15.1 ±0.61	21.8 ±0.61	15.9 ±0.49
20	26.1 ±0.53	22 ±0.53	26.5 ±0.29	21.1 ±0.87
25	31.6 ±0.53	27.3 ±0.32	31.4 ±0.68	25.5 ±0.49
30	35.9 ±0.53	31.8 ±0.53	35.9 ±0.61	30.2 ±0.28
35	41.8 ±0.32	36.8 ±0.00	38.9 ±0.57	33.4 ±0.57
40	45.8 ±0.28	41.7 ±0.53	42.8 ±0.68	37.6 ±0.55
45	50 ±0.82	45.7 ±0.32	44.2 ±0.77	40.5 ±1.72
50	53.1 ±0.83	47.3 ±1.06	47.3 ±0.29	45.3 ±0.79
55	54.4 ±1.65	50.4 ±0.94	49.3 ±0.65	47.7 ±0.78
60	55.8 ±0.82	52.5 ±0.82	51.3 ±1.43	50.7 ±0.48

TABLE – 10 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY FREEZE DRYING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	FD 1(1:1)	FD 2(1:2)	FD 3(1:3)	FD 4(1:4)
5	19±1.06	21.2±1.11	22.3±1.63	19.4±0.77
10	23.3±0.90	28.7±0.82	24.3±0.82	20.5±0.53
15	38.1±1.35	36.9±1.27	26.5±0.30	23.8±1.11
20	41.8±0.87	39.2±0.83	31.9±1.39	30.4±1.35
25	45.6±1.31	43.8±0.87	35.3±1.06	39.5±1.69
30	50.2±1.13	46.7±0.86	44.9±0.82	43.2±1.40
35	50.5±1.88	50.1±0.82	50.4±1.14	46.6±1.97
40	47.8±2.25	51.7±0.79	49.6±2.14	51.9±1.35
45	48.3±0.82	46.9±1.71	49±0.09	54.6±1.76
50	47±0.87	49.5±0.56	53.2±1.94	55.4±1.46
55	45.7±0.53	51.7±1.46	57.4±0.88	56.9±0.87
60	47.4±1.23	56±0.88	60.6±0.87	58.2±0.90

TABLE-11 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY SOLVENT EVAPORATION METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	SEM 1(1:1)	SEM 2(1:2)	SEM 3(1:3)	SEM 4(1:4)
5	10.2±1.66	6.1±4.34	10.5±1.06	6.3±4.48
10	14.7±0.97	14.4±1.10	16.5±1.63	12.5±1.98
15	21±2.35	23.3±1.11	23.4±0.68	18.1±1.61
20	28.5±1.65	29.5±1.35	32.9±1.77	26.9±1.31
25	40.6±2.17	39.5±0.57	36.9±1.58	31.5±1.02
30	41.3±1.06	54.4±0.92	44.2±0.77	36.7±1.40
35	49.4±2.04	67.5±1.63	49±1.04	42±0.80
40	52.6±3.15	77.2±0.82	54.2±0.40	46.3±1.32
45	58.6±1.30	82.8±0.96	58±0.82	50.6±1.20
50	63±0.75	58.1±0.92	61.1±1.96	52.1±2.33
55	66.3±0.75	56.2±0.83	62.6±2.03	52.5±1.14
60	69.4±1.62	54.2±1.35	63.2±2.34	51.3±1.10

TABLE -12 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PEG 6000 BY PHYSICAL MIXING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	PM1(1:1)	PM2(1:2)	PM3(1:3)	PM4(1:4)
5	5.6 ± 4.90	5.9 ± 5.12	10.7 ± 1.60	17 ± 2.37
10	9.4 ± 0.37	9.9 ± 0.70	11.4 ± 0.75	20.9 ± 1.06
15	11 ± 0.46	13 ± 0.97	16.6 ± 2.37	22.9 ± 0.96
20	14.9 ± 0.96	17.1 ± 1.06	21.4 ± 0.70	31.1 ± 2.02
25	17.7 ± 0.43	19.7 ± 0.28	25.8 ± 0.72	41.7 ± 0.75
30	19.2 ± 0.30	21.5 ± 0.46	36.8 ± 0.97	43.7 ± 0.96
35	21.9 ± 0.66	24.3 ± 0.32	43.4 ± 3.99	44.4 ± 1.70
40	24.3 ± 0.55	26.1 ± 0.65	46.9 ± 0.98	39.1 ± 1.79
45	25.9 ± 0.51	27.5 ± 0.37	46.1 ± 1.28	40.9 ± 0.70
50	27.9 ± 0.61	28± 0.65	43.5 ± 2.84	41.3 ± 0.60
55	29.4 ± 0.36	29.4 ± 0.92	42.2 ± 0.97	44.4 ± 0.60
60	31.5 ± 0.26	30.6 ± 0.60	42.4 ± 0.65	45.9± 1.30

TABLE - 13 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY PHYSICAL MIXING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	PM5(1:1)	PM6(1:2)	PM7(1:3)	PM8(1:4)
5	10.9 ± 1.60	2.8 ± 4.90	12.4 ± 0.65	2.8 ± 4.00
10	16.3 ± 1.34	12 ± 1.36	16.7 ± 1.50	9.4 ± 0.32
15	17.7 ± 1.36	15.9 ± 1.35	21.9 ± 2.37	12.3 ± 0.78
20	19.7 ± 0.80	19.5 ± 1.65	24.4 ± 0.32	17.3 ± 0.53
25	28.7 ± 1.50	24.8 ± 0.70	30.1 ± 1.53	22.3 ± 0.32
30	31.4 ± 2.35	27 ± 0.65	30.2 ± 2.25	26.3 ± 0.53
35	35.7 ± 0.97	29.7 ± 1.97	32.3 ± 1.70	29.4 ± 0.32
40	38.3 ± 1.55	33.8 ± 2.04	37 ± 0.32	32.3 ± 0.30
45	40.4 ± 1.30	37.7 ± 0.43	39.6 ± 1.09	35.3 ± 0.78
50	40.6 ± 3.69	38.9± 1.81	41.1 ± 0.80	36.8 ± 0.53
55	42.4 ± 1.35	38.1± 1.35	40.4 ± 0.05	37.2 ± 0.53
60	43.1 ± 1.65	38.7± 0.43	40 ± 0.96	37.5± 0.97

TABLE- 14 CUMULATIVE % DRUG RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 BY PHYSICAL MIXING METHOD

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	PM9(1:1)	PM 10(1:2)	PM 11(1:3)	PM 12(1:4)
5	5.9 ± 4.18	8.9 ± 0.61	9.4 ± 0.82	11.3 ± 0.79
10	13.3 ± 0.86	14.7 ± 0.79	15.8 ± 0.53	16.3 ± 0.28
15	18.3 ± 0.26	20.8 ± 0.32	21.7 ± 1.44	20.6 ± 0.53
20	21.6 ± 0.79	23.5 ± 1.06	25.6 ± 0.83	24.3 ± 0.30
25	24.7 ± 0.30	26.8 ± 0.28	32.5 ± 0.87	28.8 ± 0.30
30	29.1 ± 0.57	30.8 ± 0.32	36.4 ± 0.28	32.6 ± 0.53
35	33 ± 0.35	36.2 ± 0.57	40.9 ± 1.10	36.9 ± 1.10
40	37 ± 0.61	40.7 ± 0.83	45.1 ± 0.30	43.7 ± 0.35
45	42.9 ± 0.78	43.5 ± 0.53	48 ± 0.26	47.6 ± 0.53
50	44.2 ± 0.26	46.7 ± 0.57	50.3 ± 0.57	47.9 ± 0.26
55	46 ± 0.30	50 ± 0.28	50.8 ± 0.48	49.8 ± 1.27
60	47.8 ± 0.30	52.3 ± 0.57	52.2 ± 0.29	51.1± 0.57

TABLE - 15 COMPARISION OF SOLUBILITY STUDY OF RACECADOTRIL USING DISTILLED WATER AND ACID BUFFER pH 1.2

S.NO	FORMULATION	DISTILLED WATER (mg/ml)	ACID BUFFER pH 1.2 (mg/ml)
1	PURE DRUG	0.076	0.103
2	PHYSICAL MIXTURE (Drug:PVP K30 1:3)	0.110	0.161
3	SOLID DISPERSION (KM 7)	0.160	0.344

TABLE - 16 COMPARISIONOF *IN-VITRO* RELEASE PROFILE OF BEST FORMULATION (KM7) WITH MARKETED FORMULATION

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*		
	PURE DRUG	KM 7 (1:3)	MARKETED CAPSULE
5	5.6±4.90	9.6 ± 0.61	19.2 ± 1.66
10	9.4±0.37	13.4 ± 0.82	22.1 ± 0.46
15	11.5±1.06	18.4 ± 0.63	23.7 ± 0.81
20	12.9±1.02	23 ± 0.82	26.8 ± 2.20
25	15.3±0.98	48.8 ± 1.74	30.6 ± 0.66
30	18.5±0.32	53.6± 0.53	34.6 ± 0.73
35	22.5±0.60	56.3 ± 0.53	36.8 ± 0.94
40	24.9±0.43	60.4± 0.83	39 ± 1.02
45	25.6±0.70	64.4 ± 0.83	41.5 ± 1.05
50	26.1±0.43	67.3 ± 0.35	43.5 ± 0.79
55	27.4±0.05	70 ± 0.63	44.2 ± 0.10
60	28.1±0.32	72.7 ± 0.35	44.8 ± 0.87

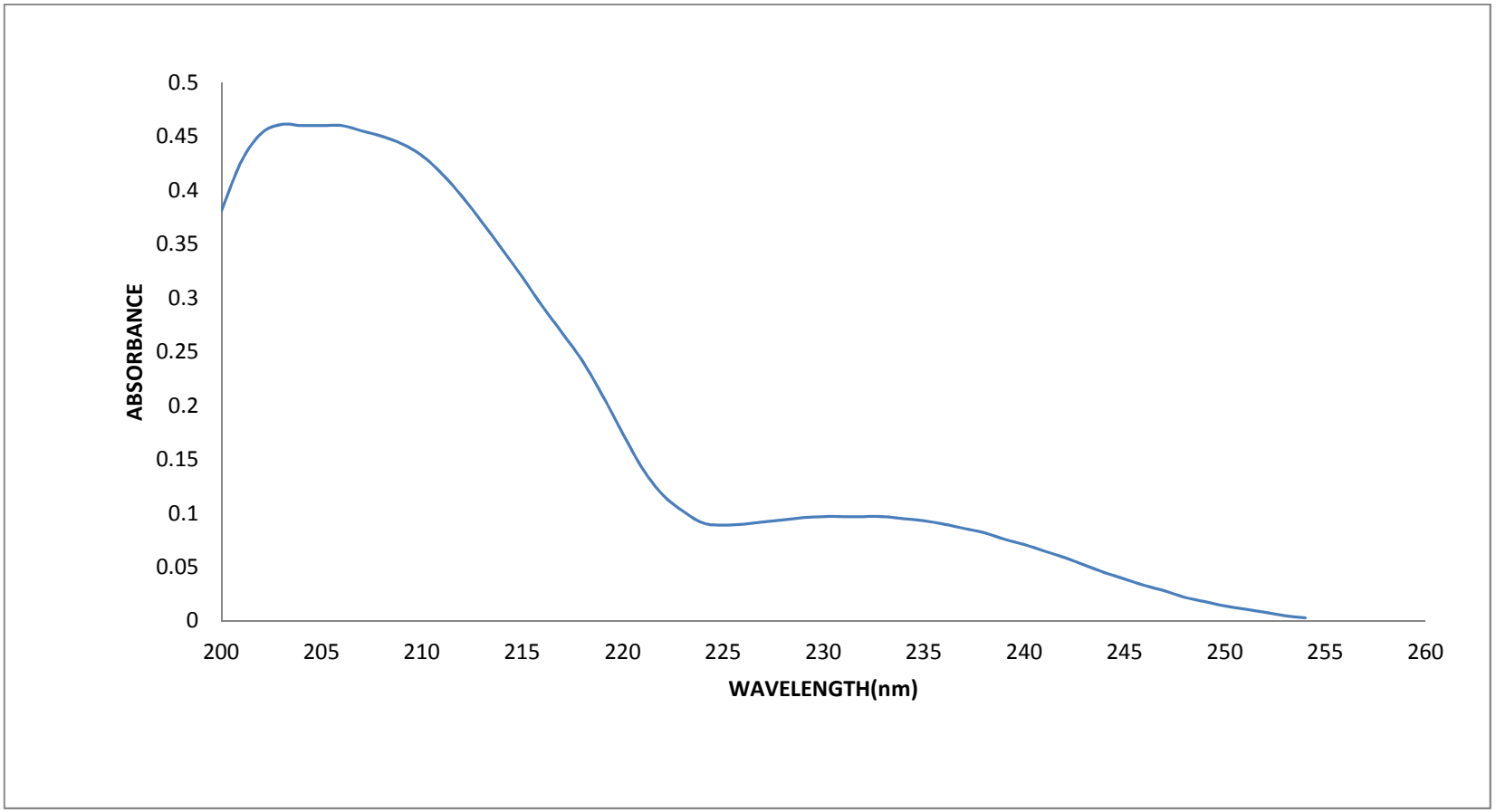


FIGURE 1-A DETERMINATION OF λ max OF RACECADOTRIL

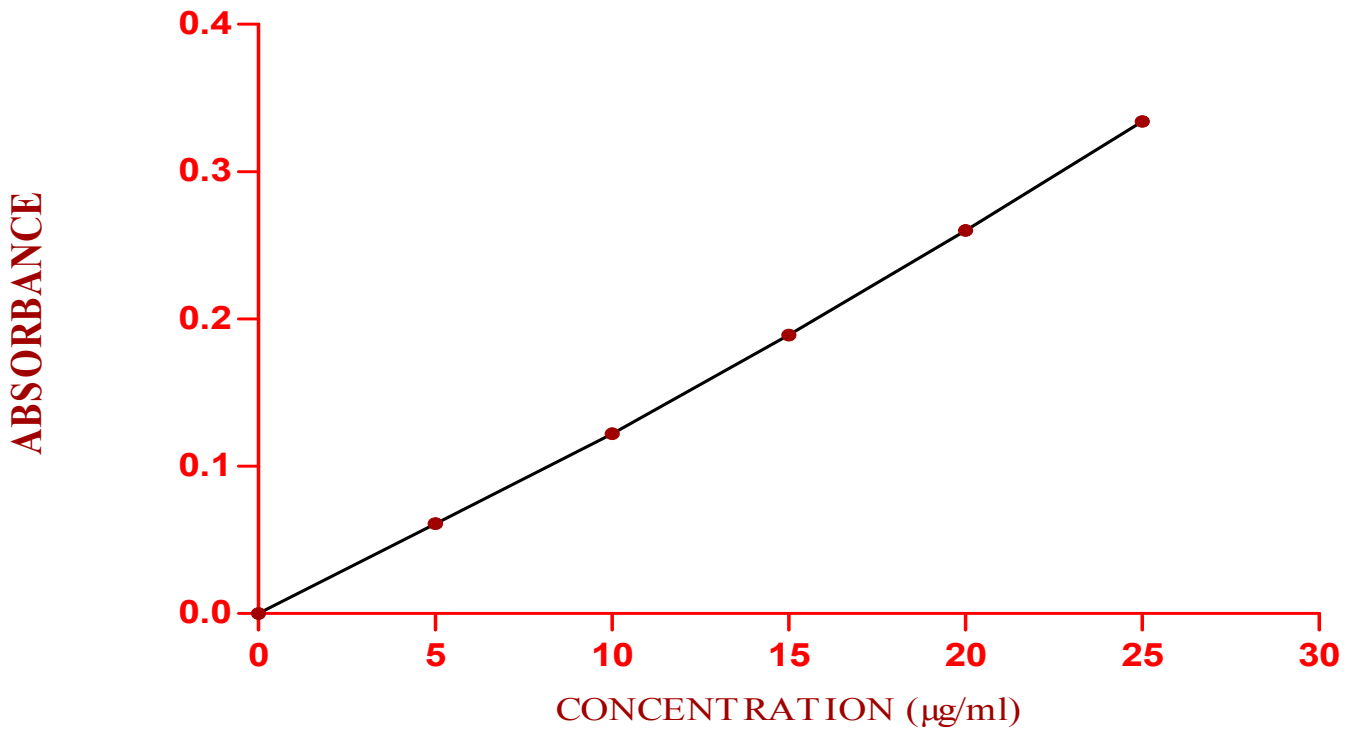


Figure- 1-B CALIBRATION OF RACECADOTRIL (pH 1.2)

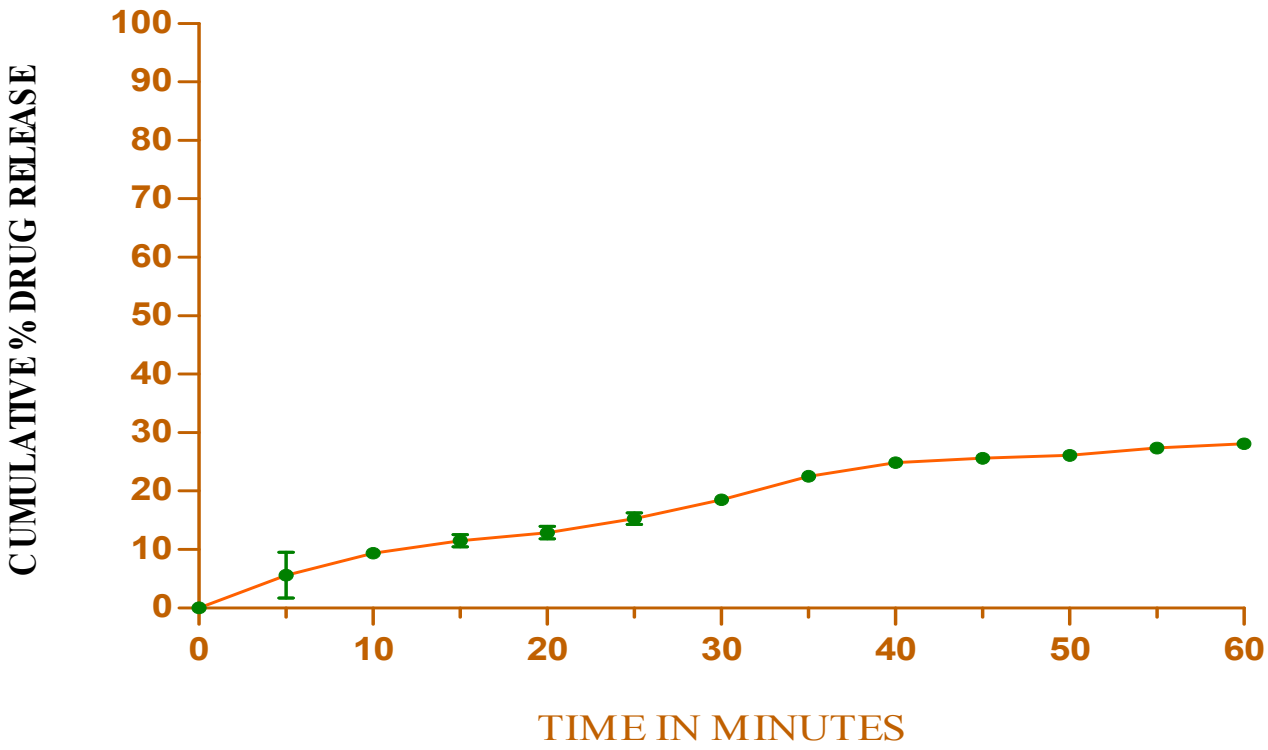


Figure- *2 IN-VITRO* RELEASE PROFILE OF RACECADOTRIL (PURE DRUG)

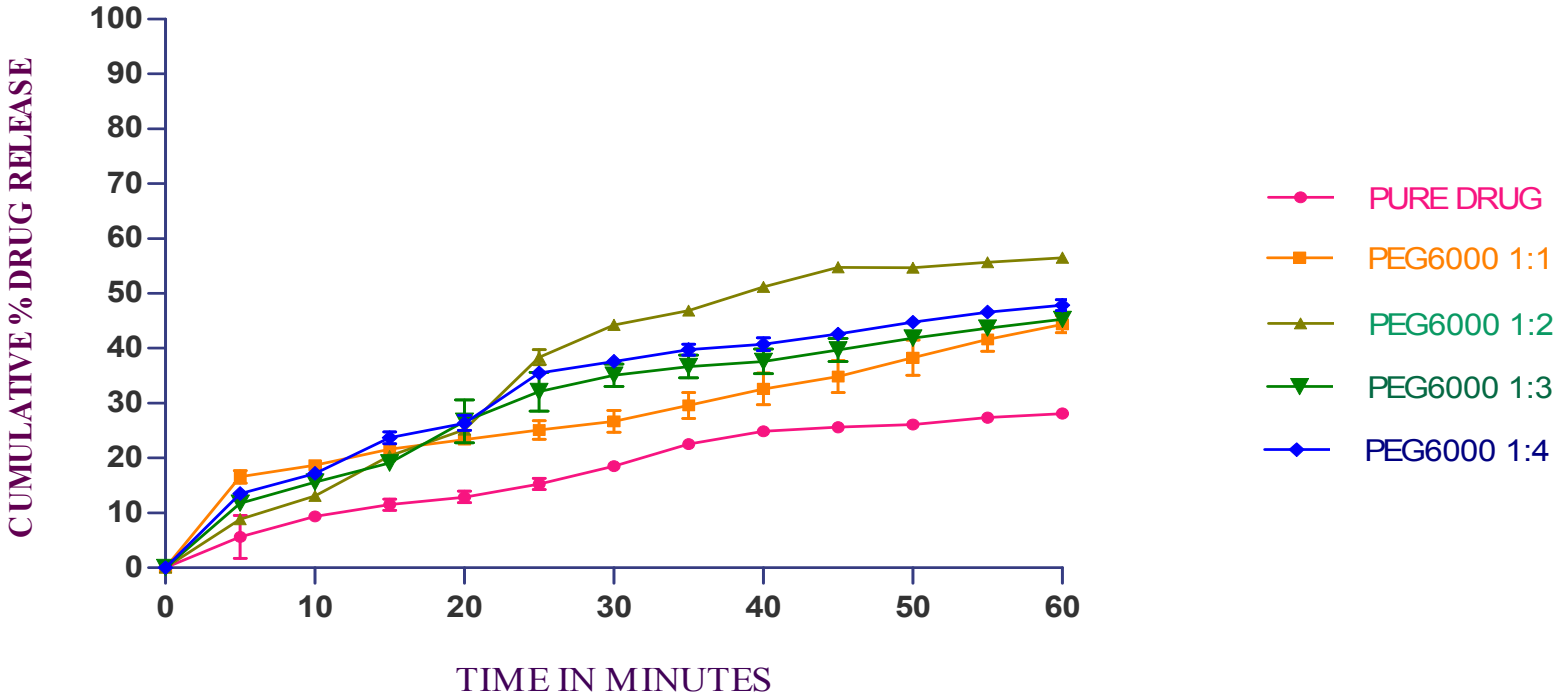


Figure-3 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PEG6000 BY KNEADING METHOD

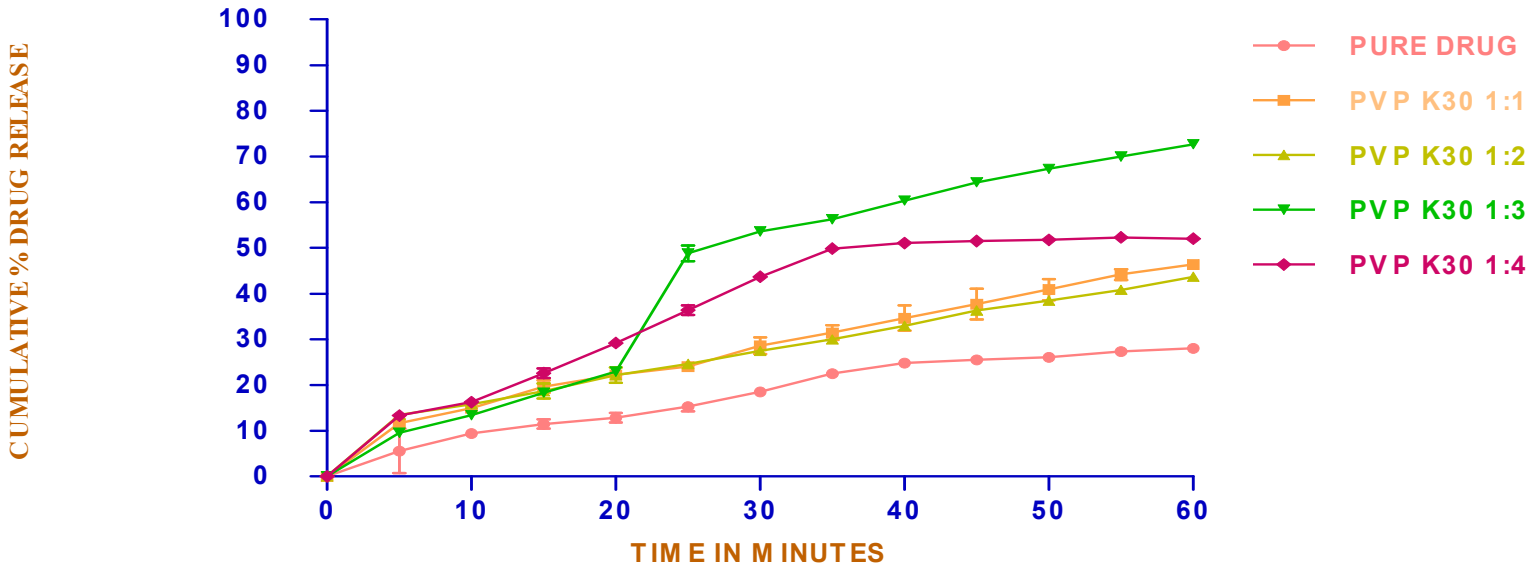


Figure-4 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY KNEADING METHOD

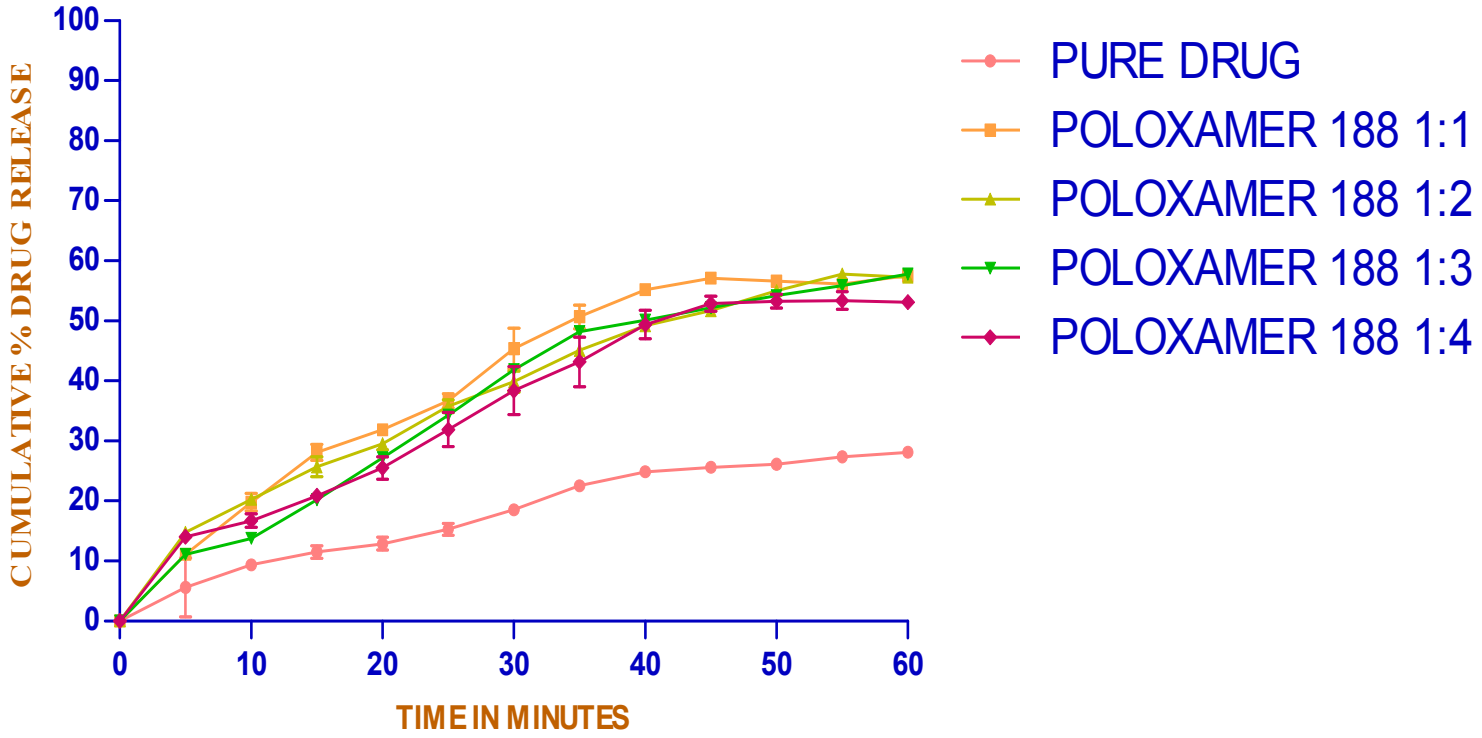


Figure-5 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 BY KNEADING METHOD

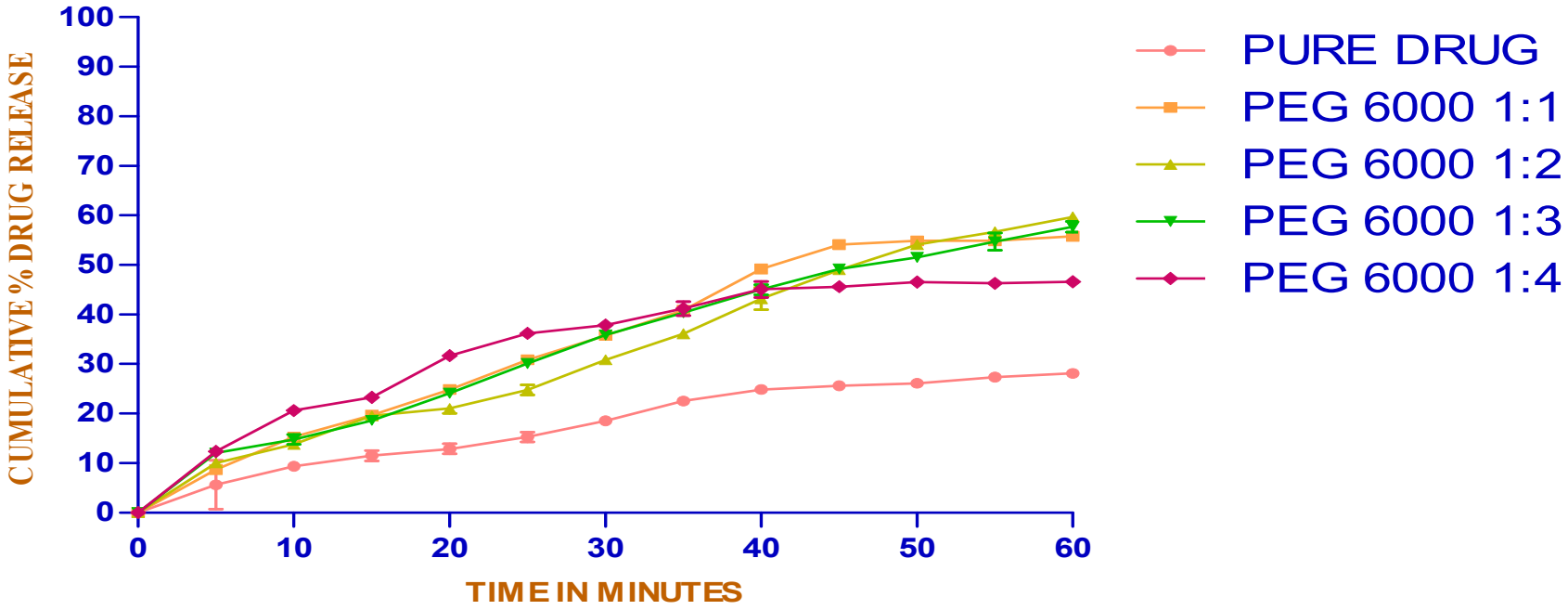


Figure-6 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PEG6000 BY MELTING METHOD

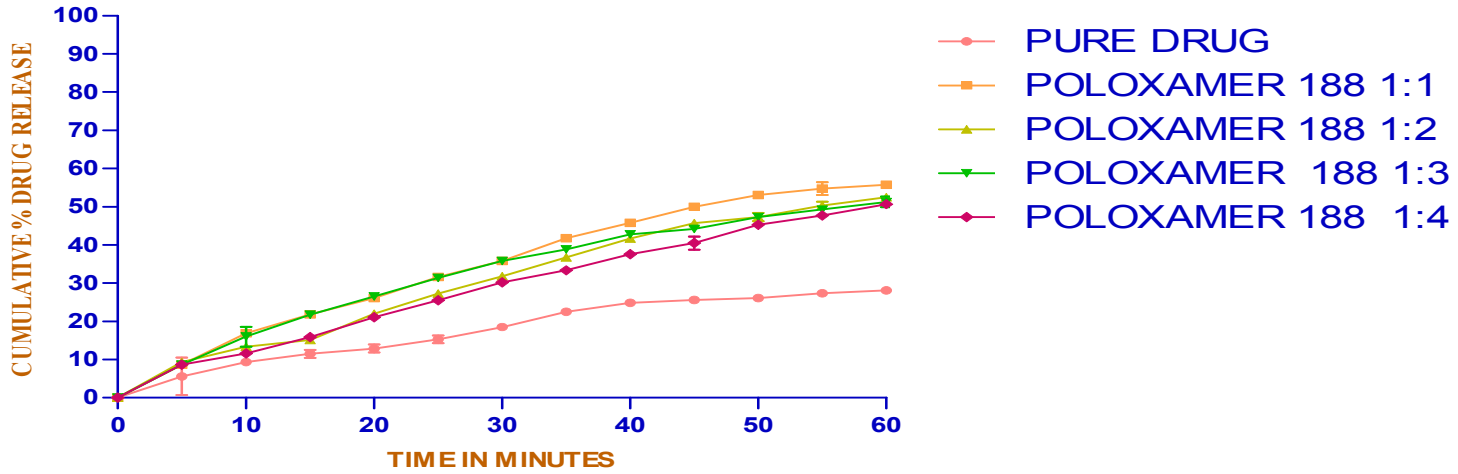


Figure-7 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 BY MELTING METHOD

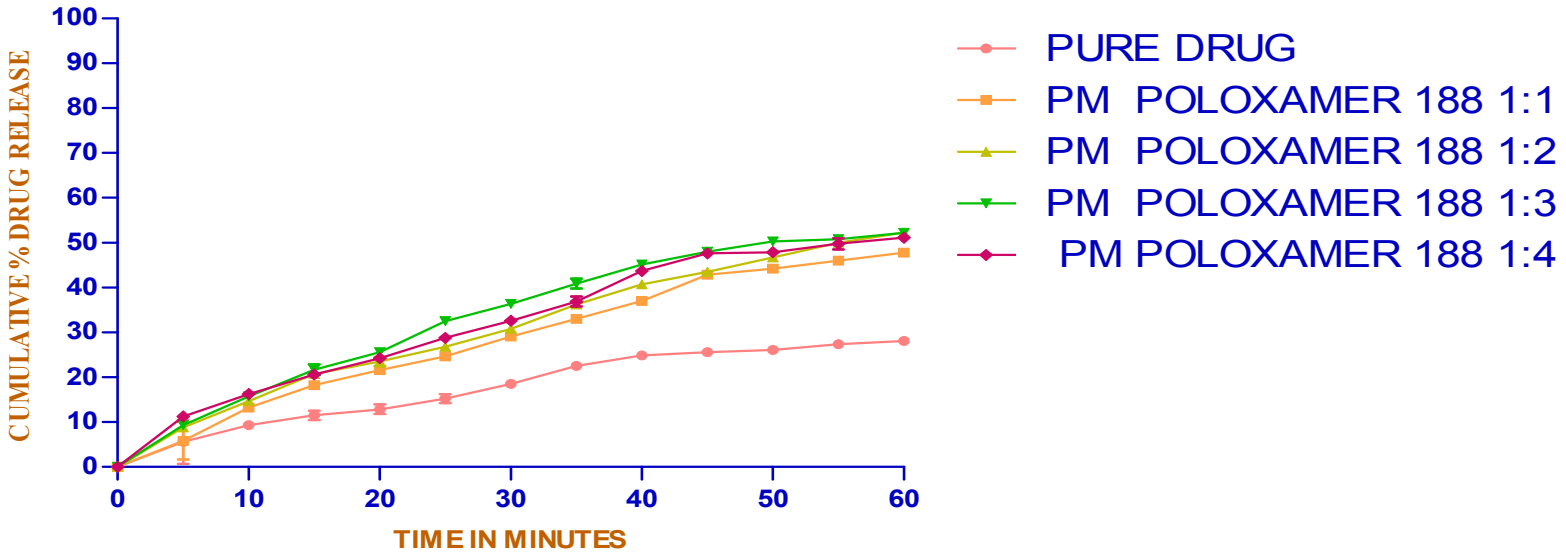


Figure-8 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING POLOXAMER 188 (PHYSICAL MIXTURE)

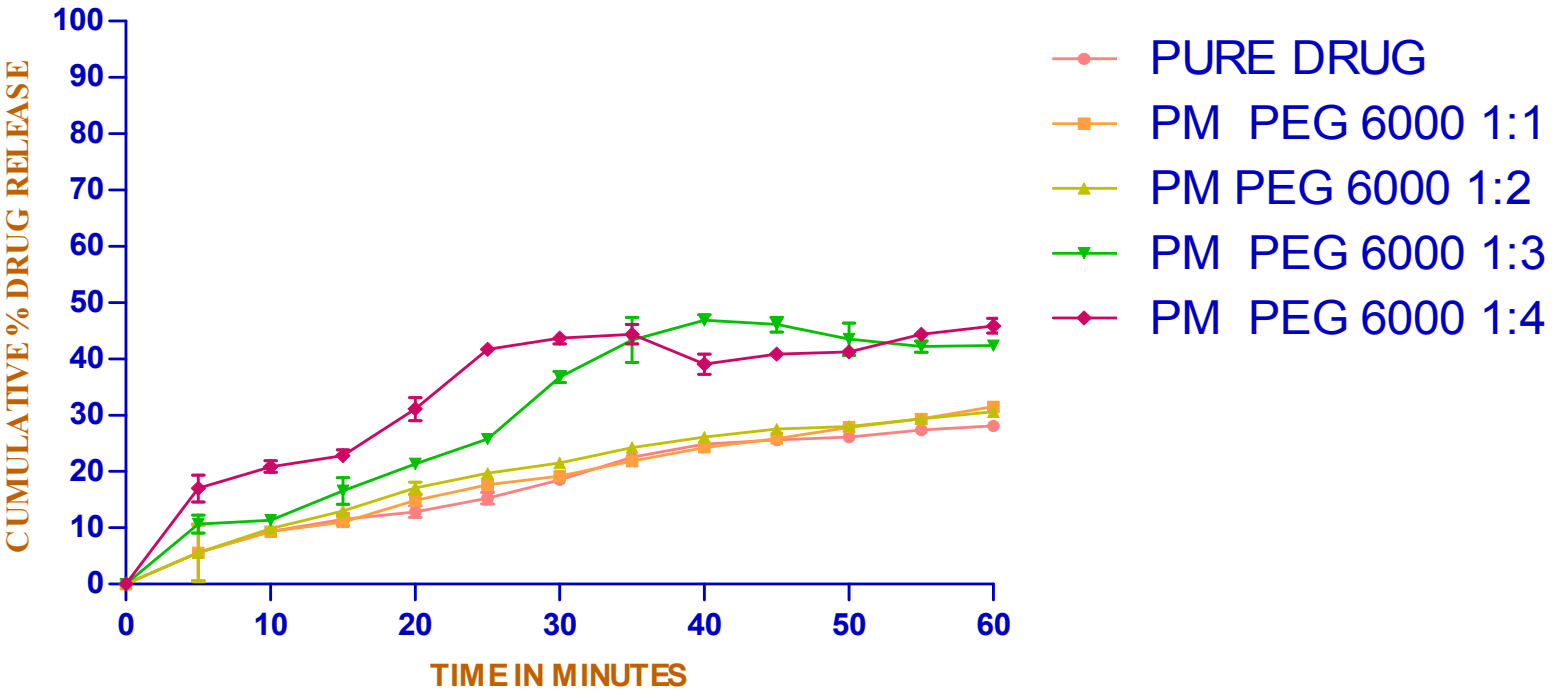


Figure-9 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PEG 6000 (PHYSICAL MIXTURE)

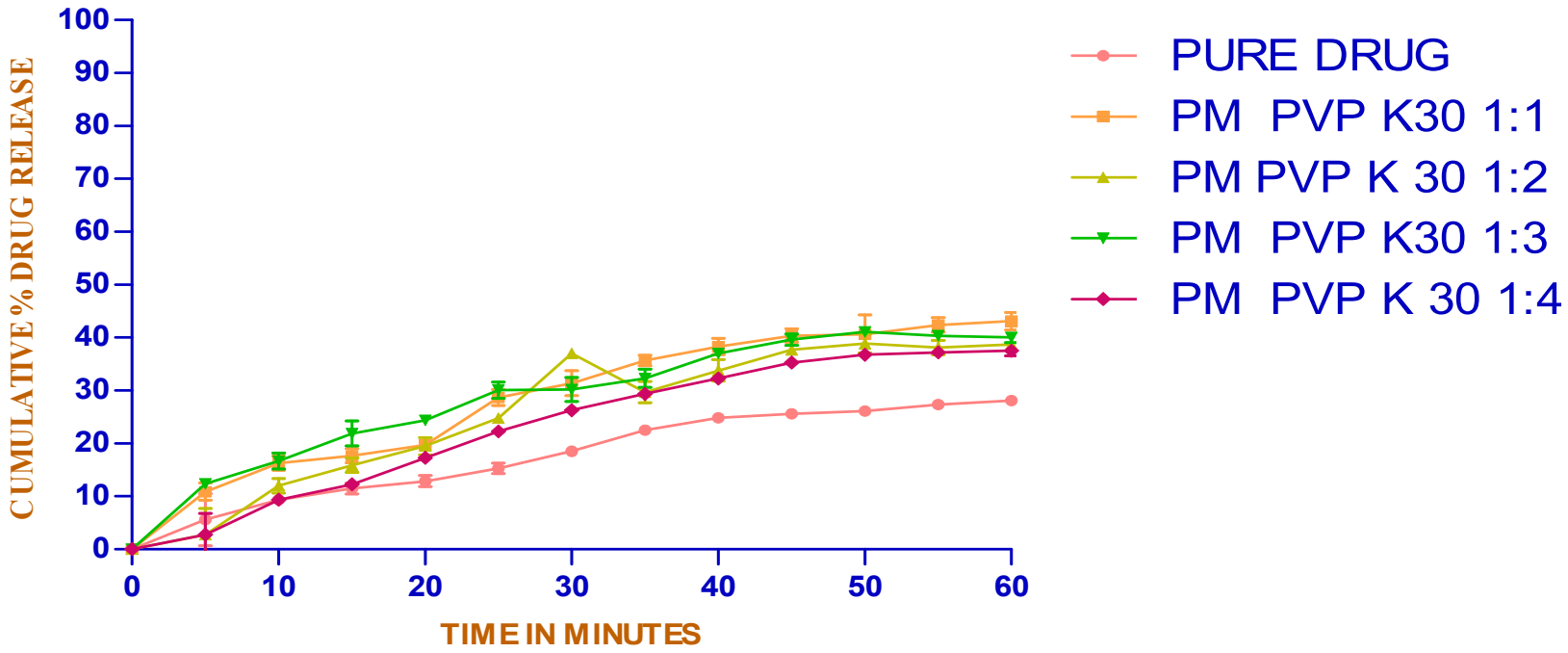


Figure-10 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PVP K30 (PHYSICAL MIXTURE)

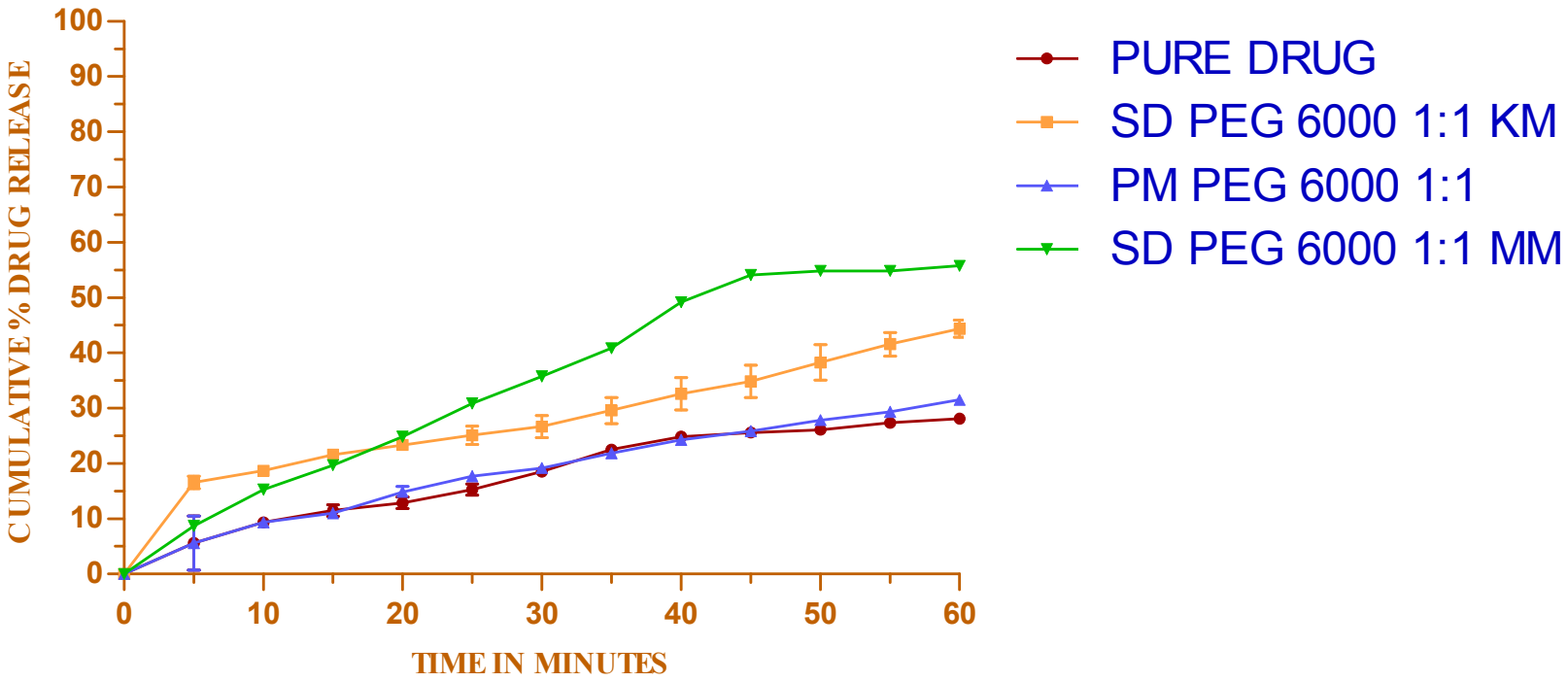


Figure-11 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PEG 6000(1:1)

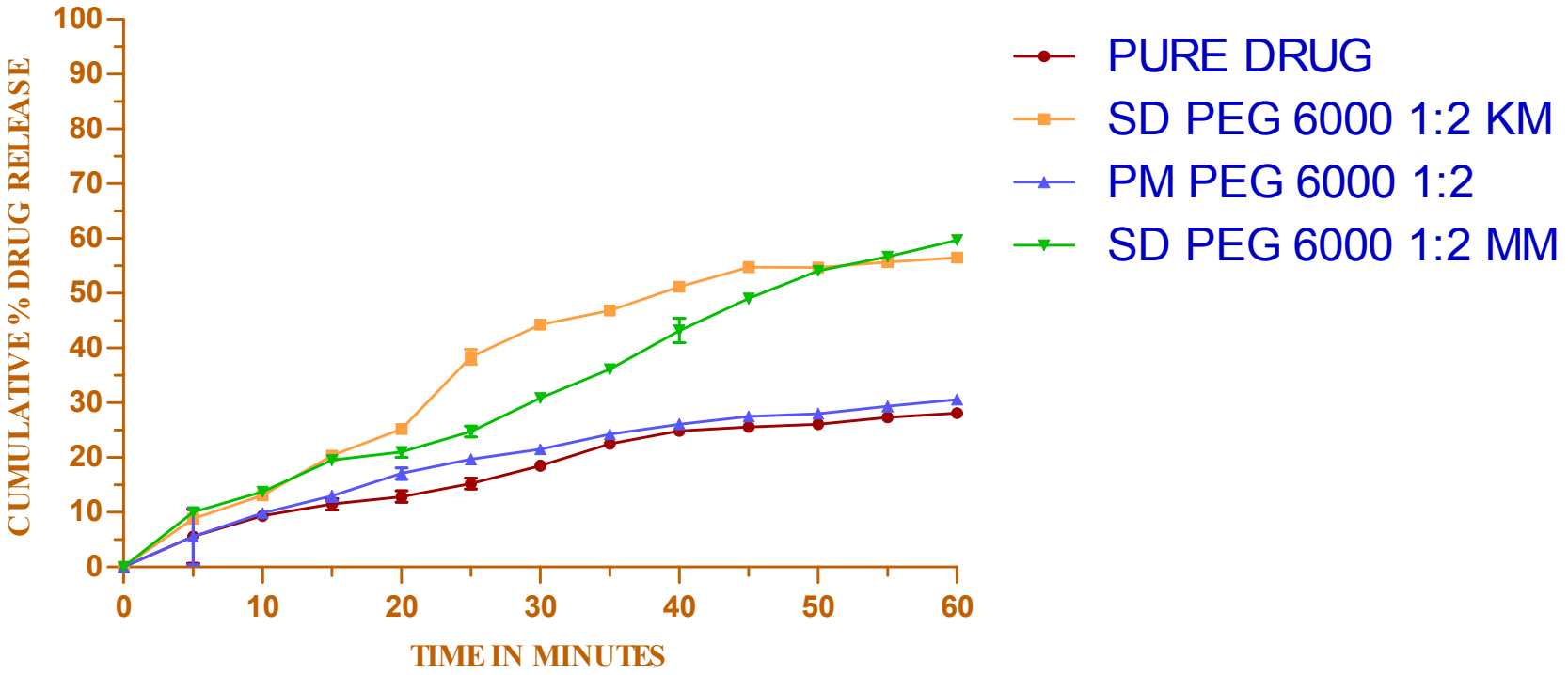


Figure-12 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PEG 6000(1:2)

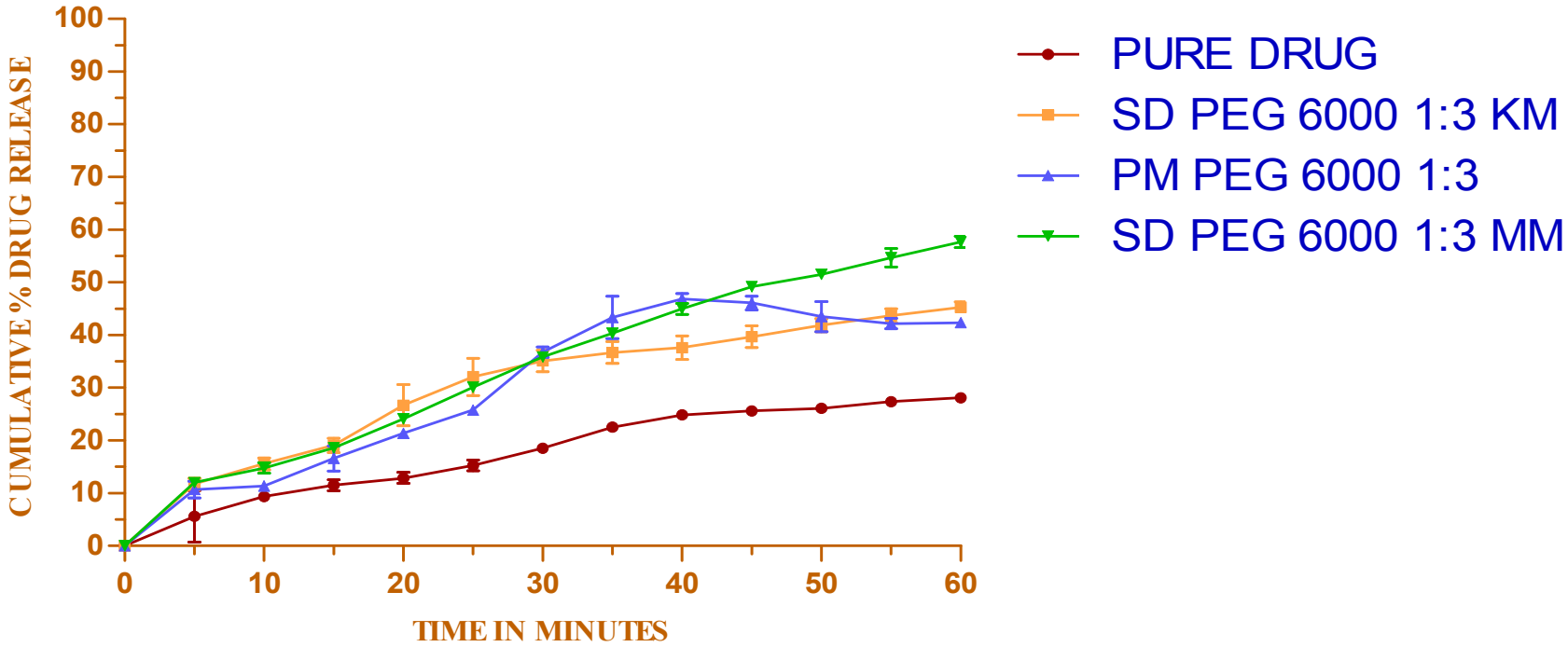


Figure-13 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PEG 6000(1:3)

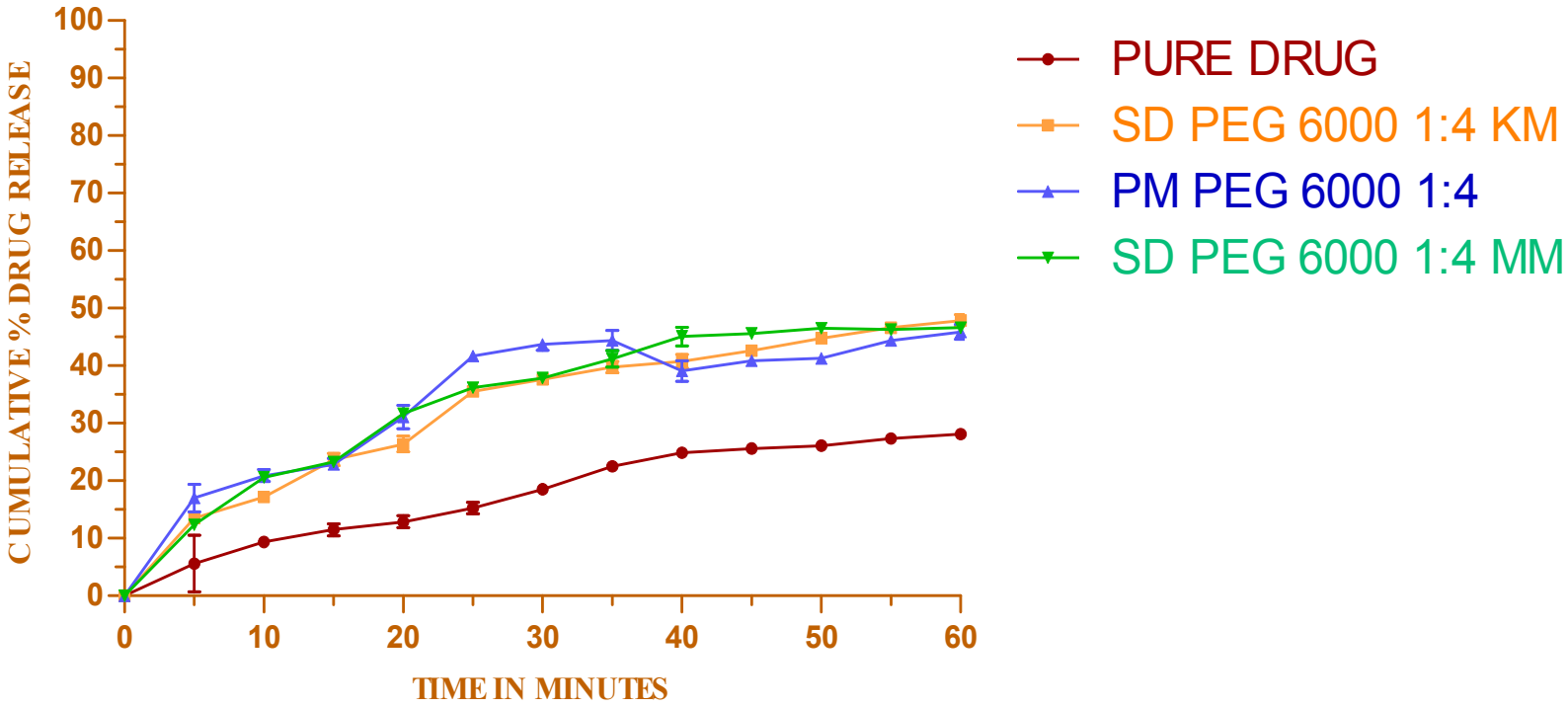


Figure-14 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PEG 6000(1:4)

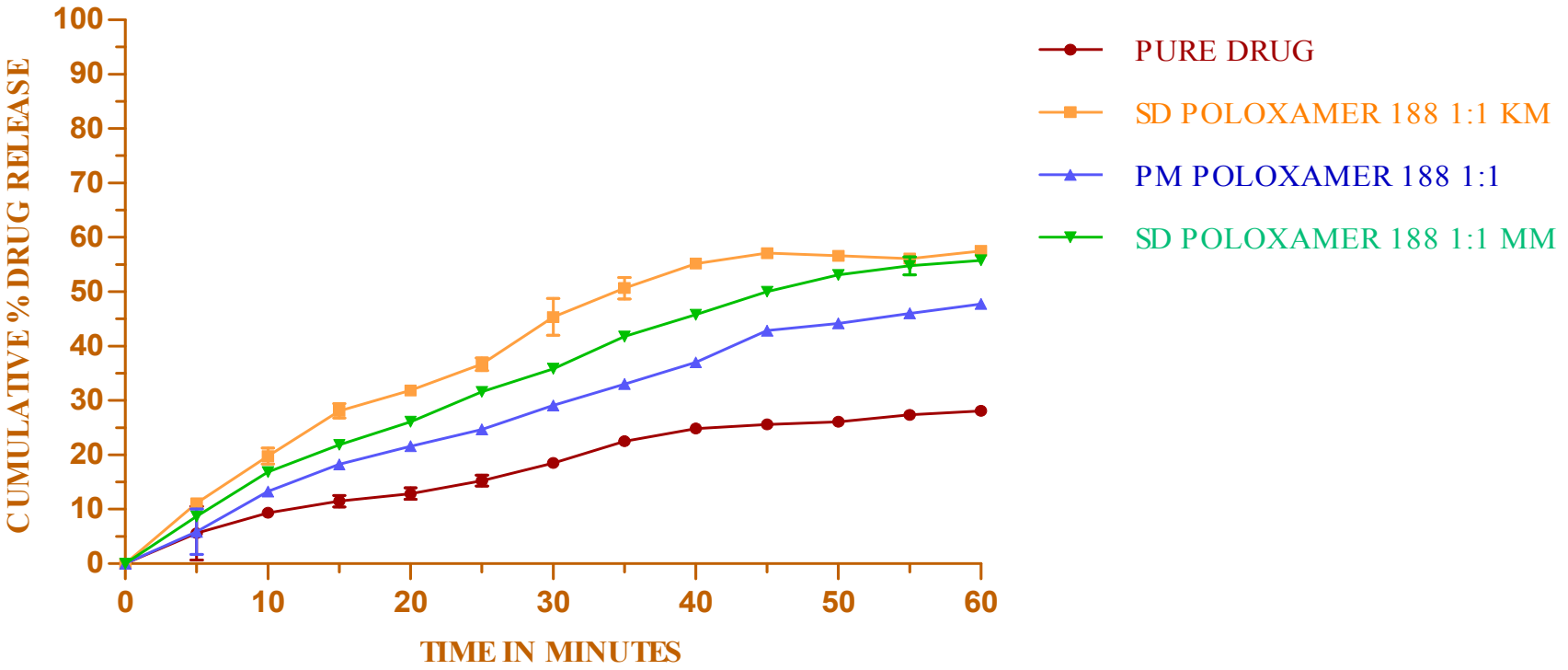


Figure-15 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING POLOXAMER 188 (1:1)

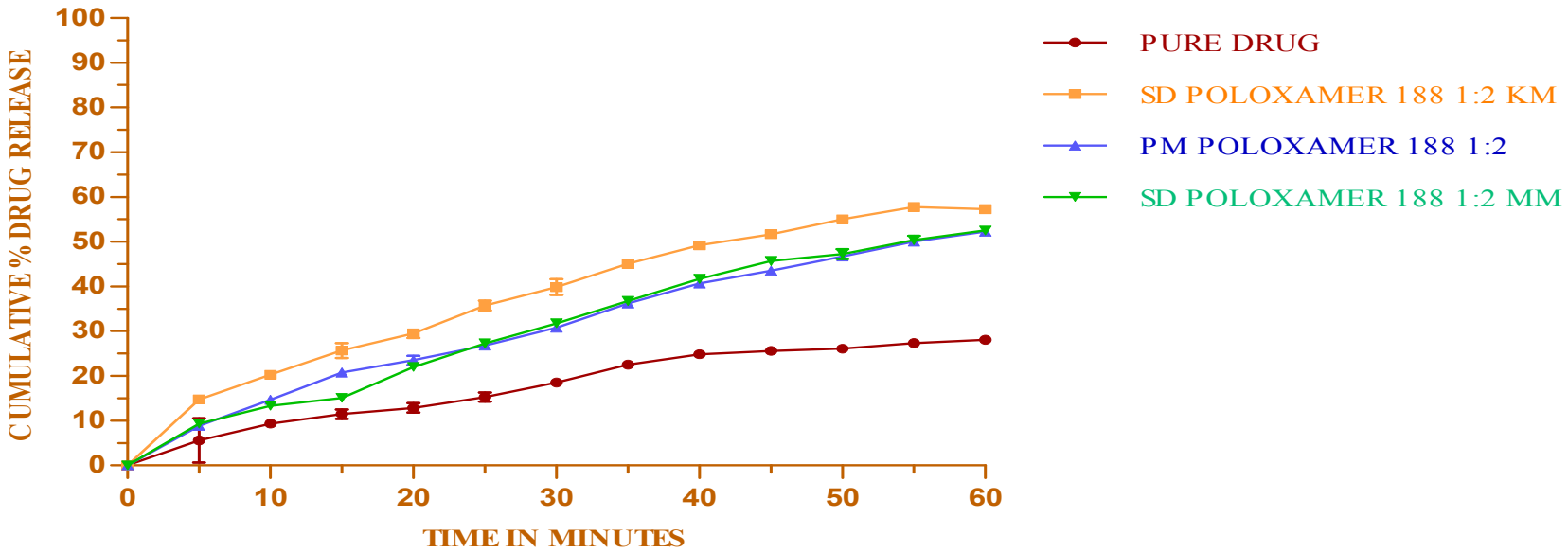


Figure-16 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING POLOXAMER 188 (1:2)

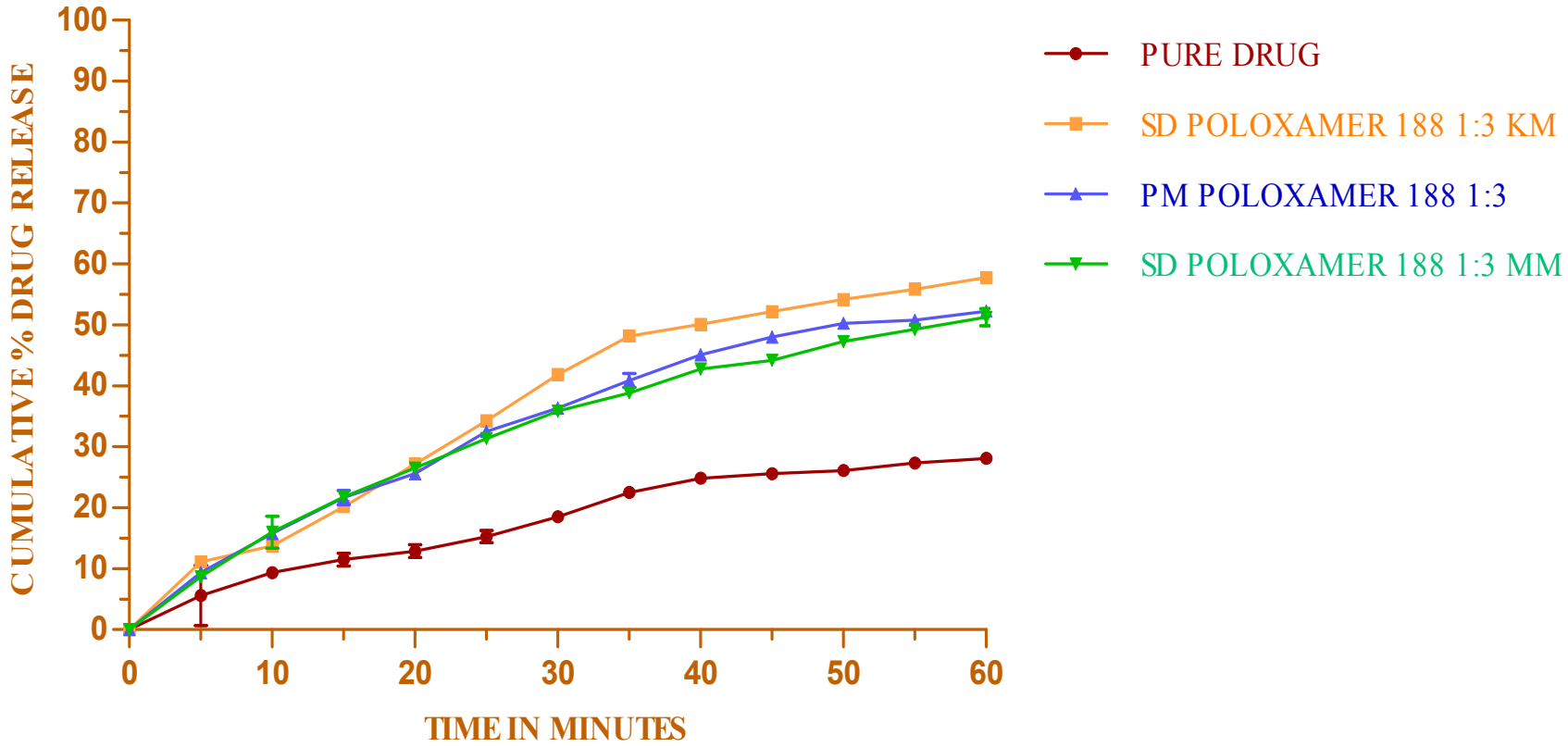


Figure-17 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING POLOXAMER 188 (1:3)

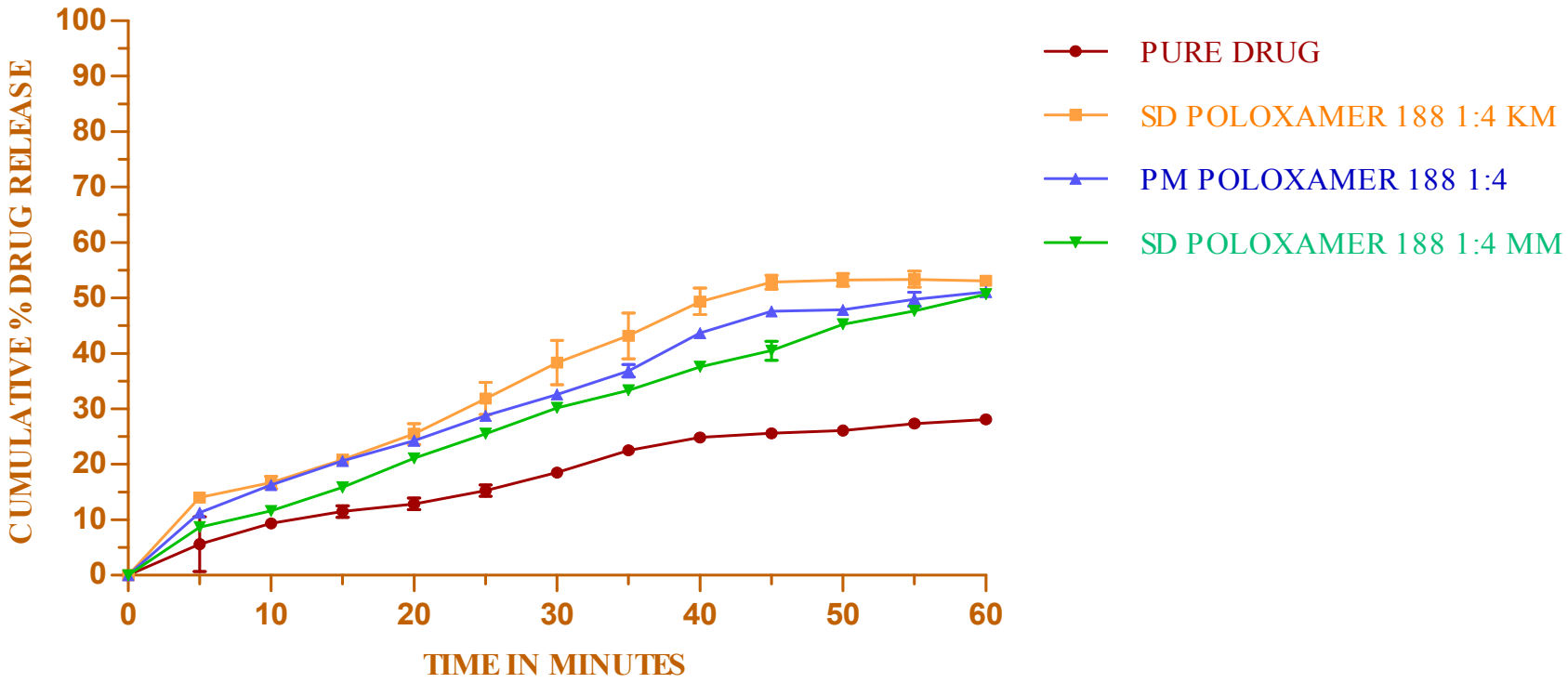


Figure-18 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING POLOXAMER 188 (1:4)

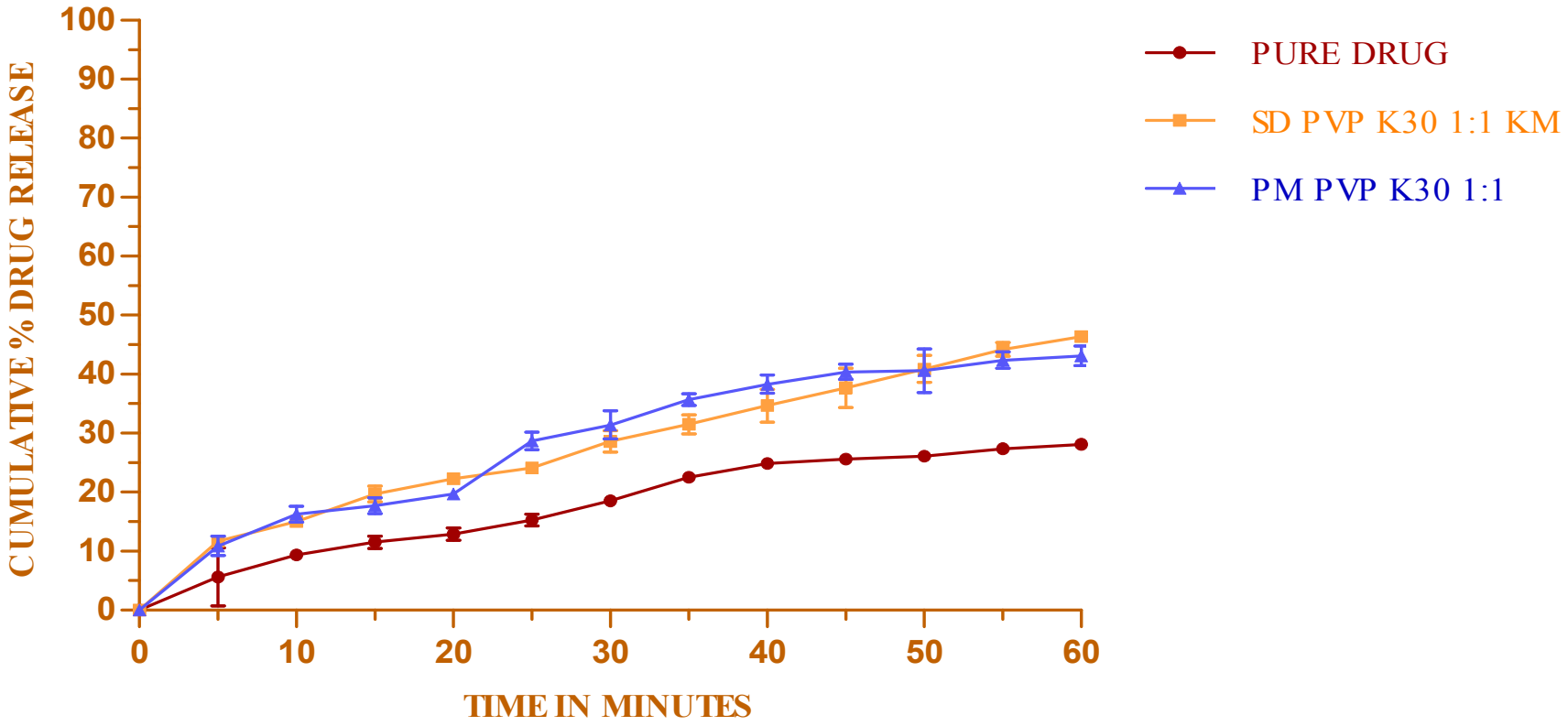


Figure-19 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PVP K30 (1:1

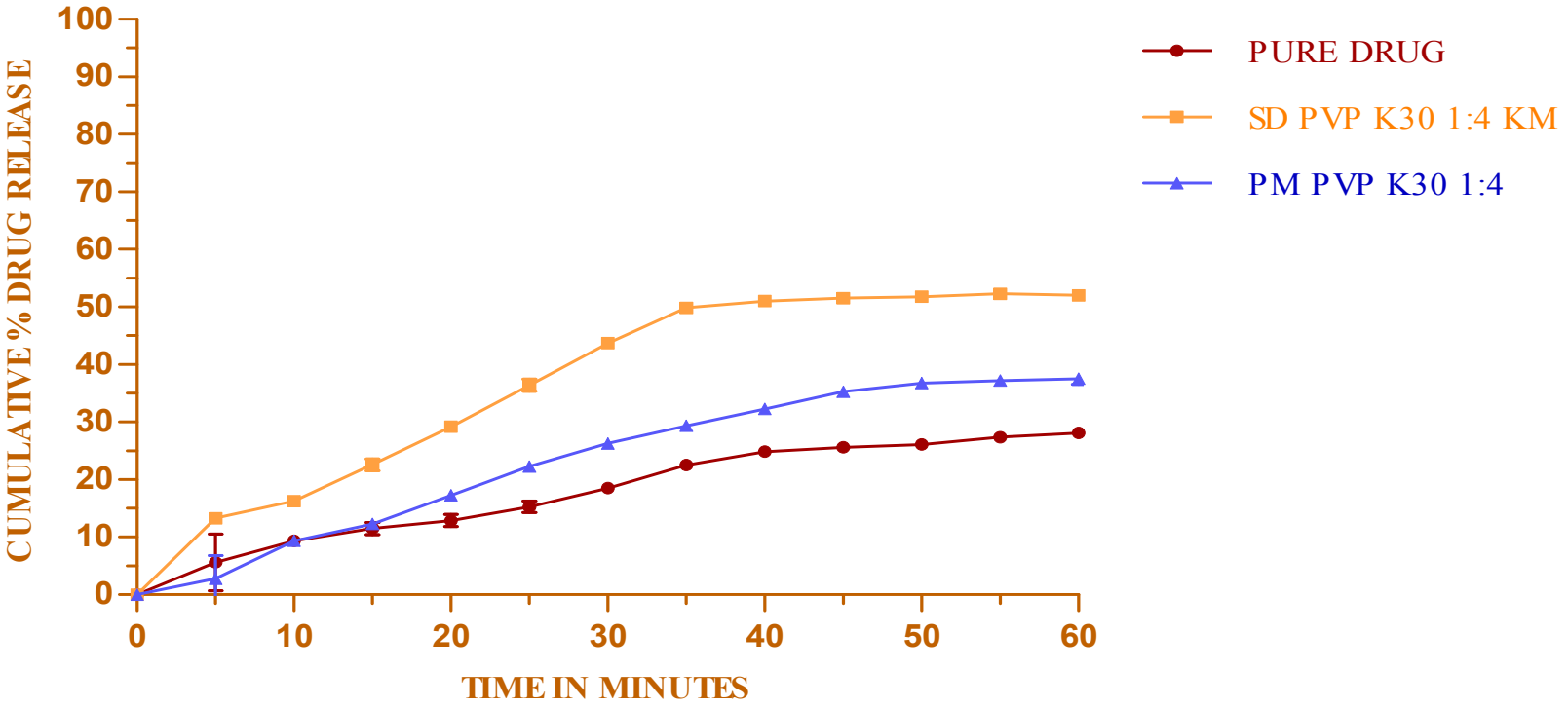


Figure-22 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PVP K30 (1:4)

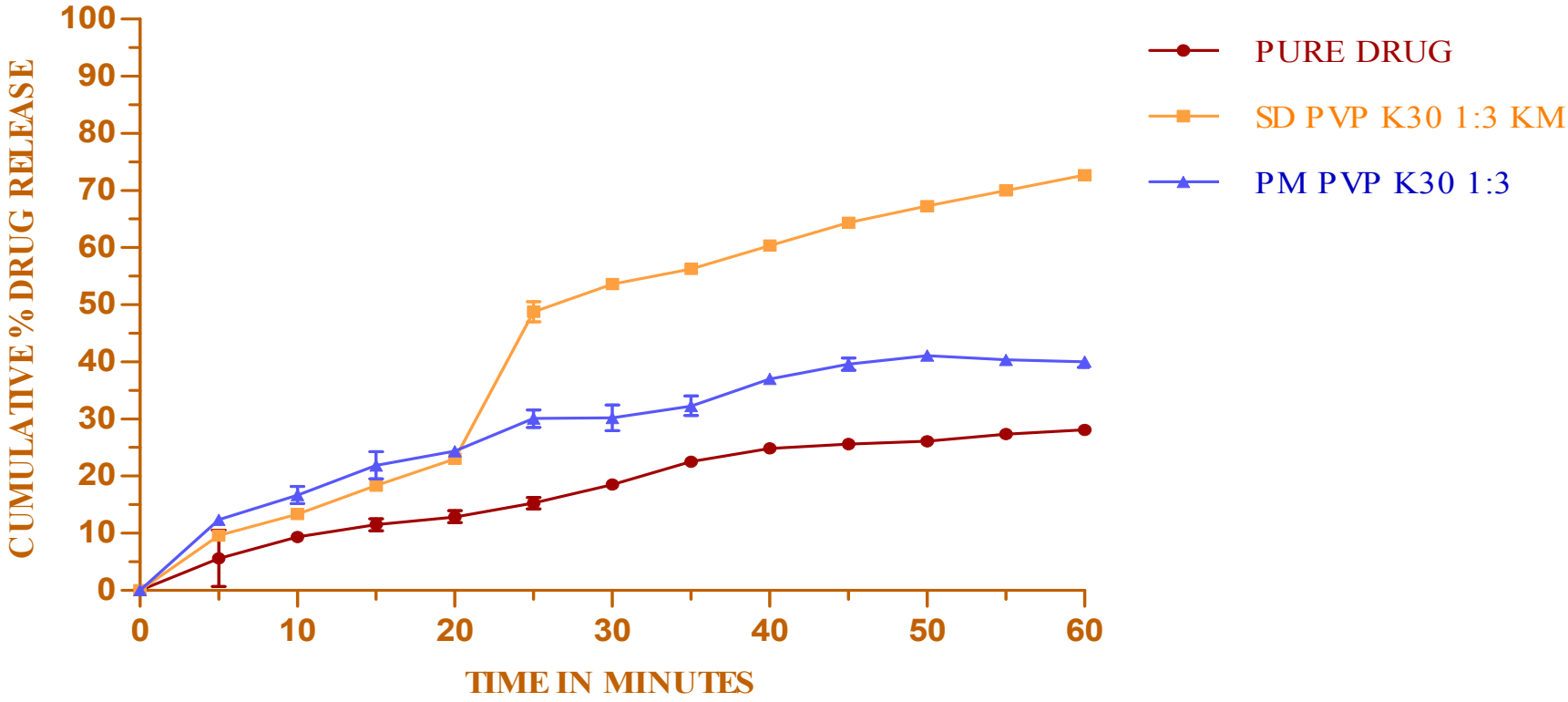


Figure-21 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PVP K30 (1:3)

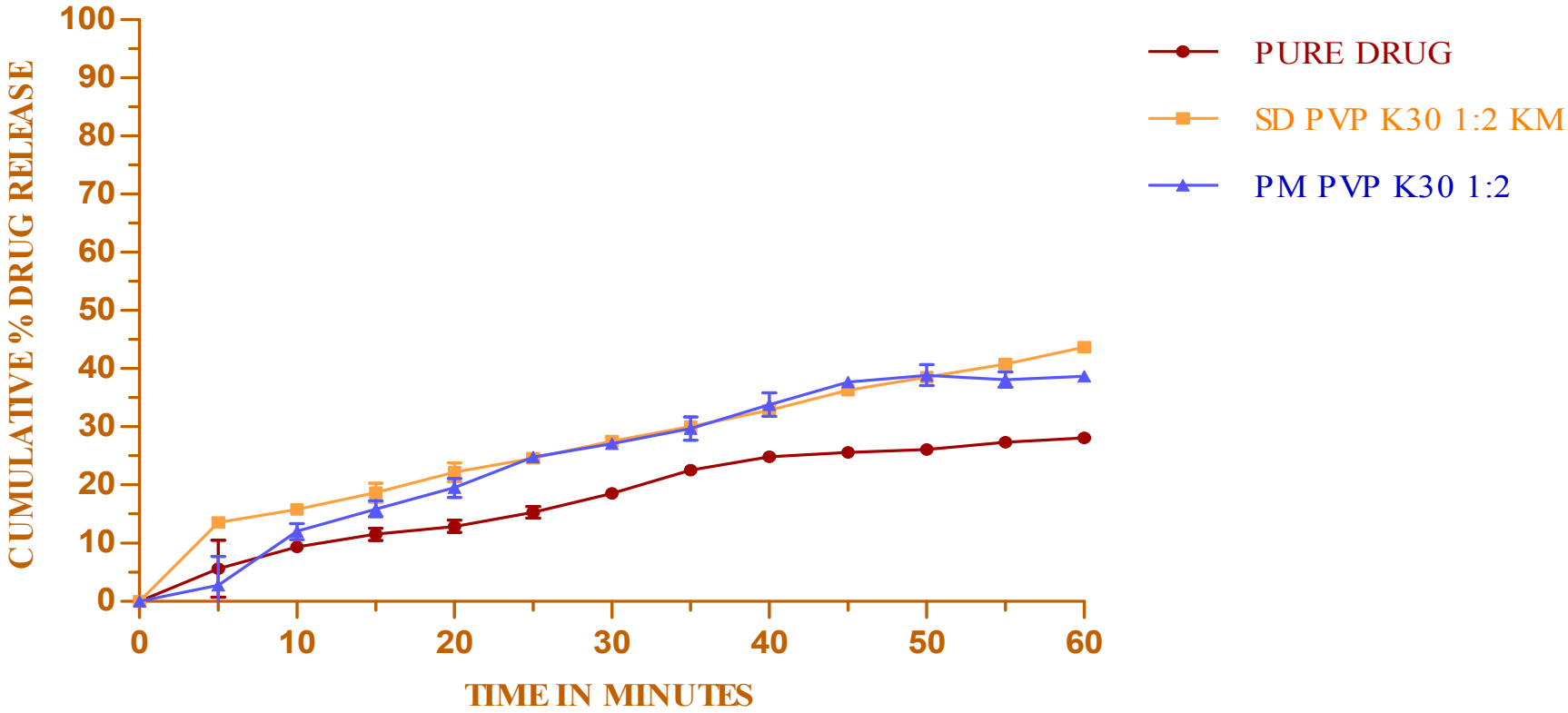


Figure-20 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL PURE DRUG WITH SILID DISPERSION AND PHYSICAL MIXTURE USING PVP K30 (1:2)

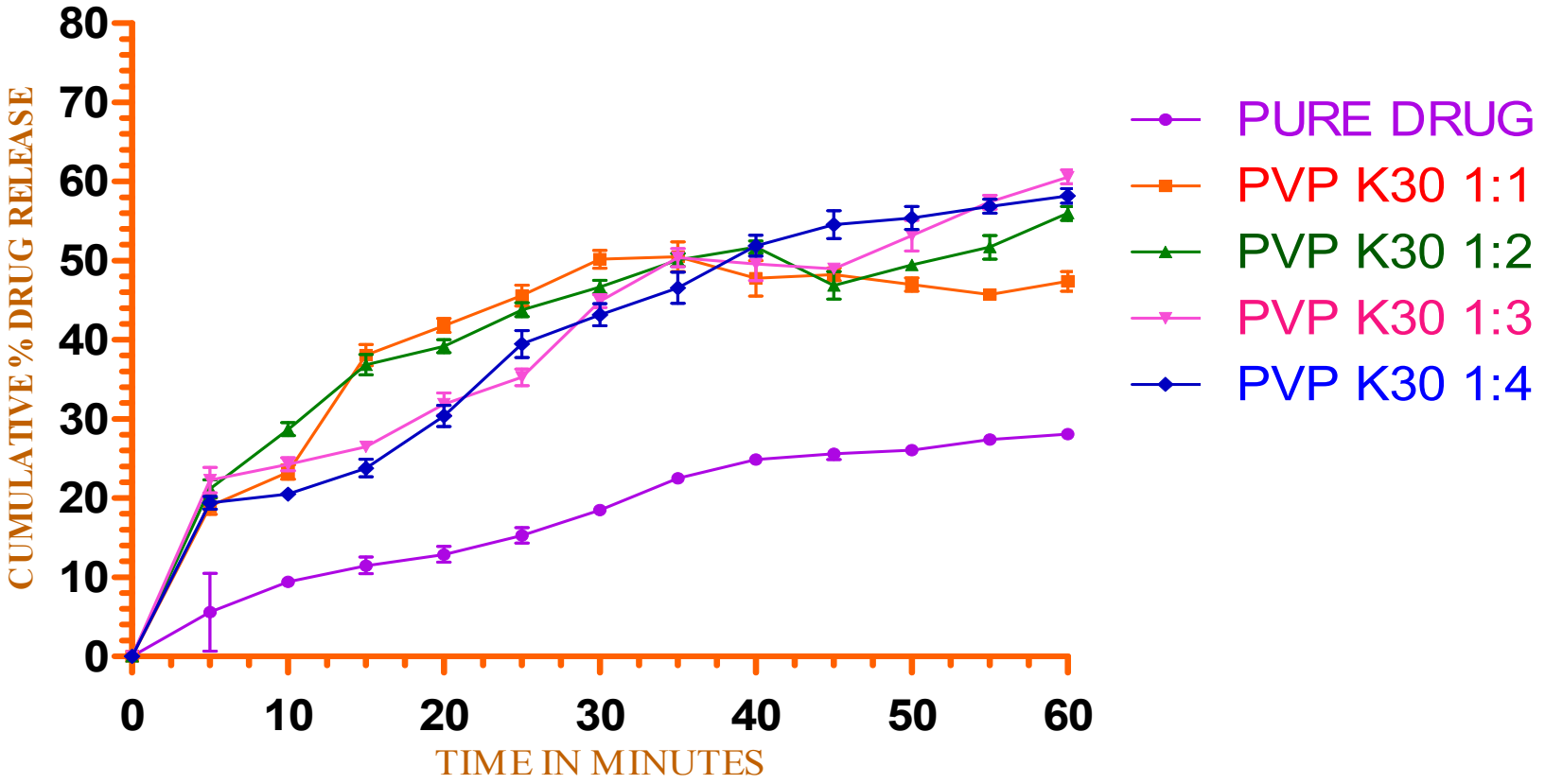


Figure-23 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY FREEZE DRYING MEYHOD

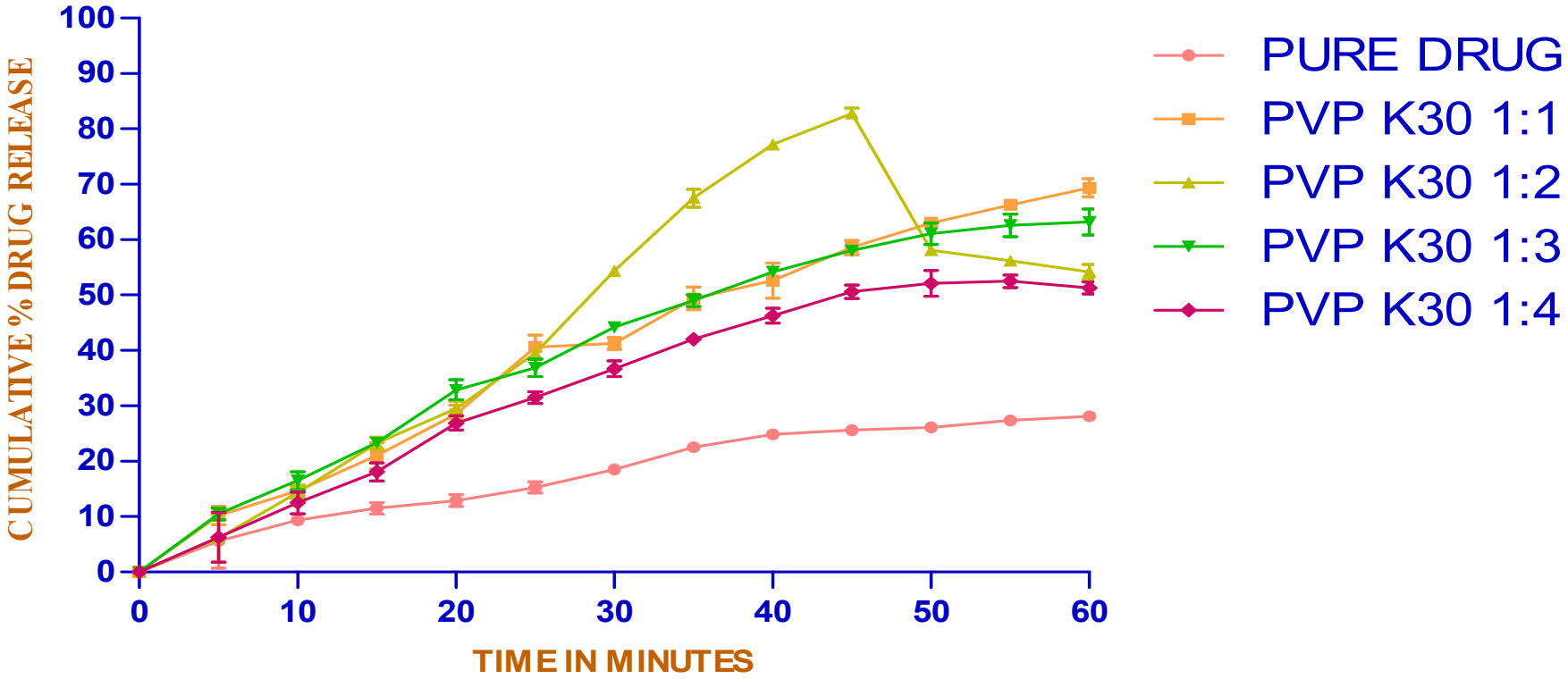


Figure-24 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL USING PVP K30 BY SOLVENT EVAPORATION MEYHOD

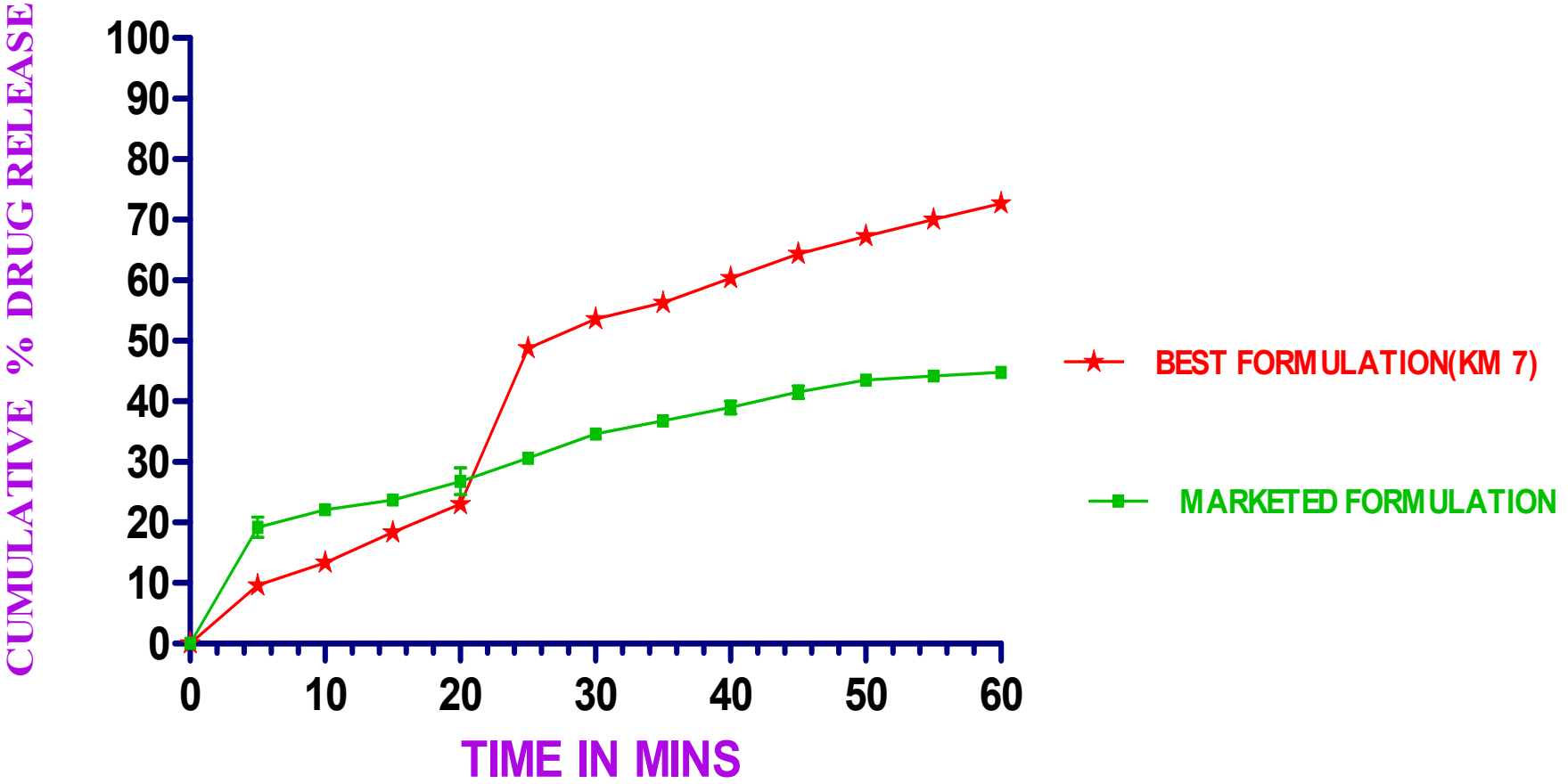


Figure-25 COMPARISON OF *IN-VITRO* RELEASE PROFILE OF RACECADOTRIL MARKETED CAPSULES WITH BEST FORMULATION (KM 7)

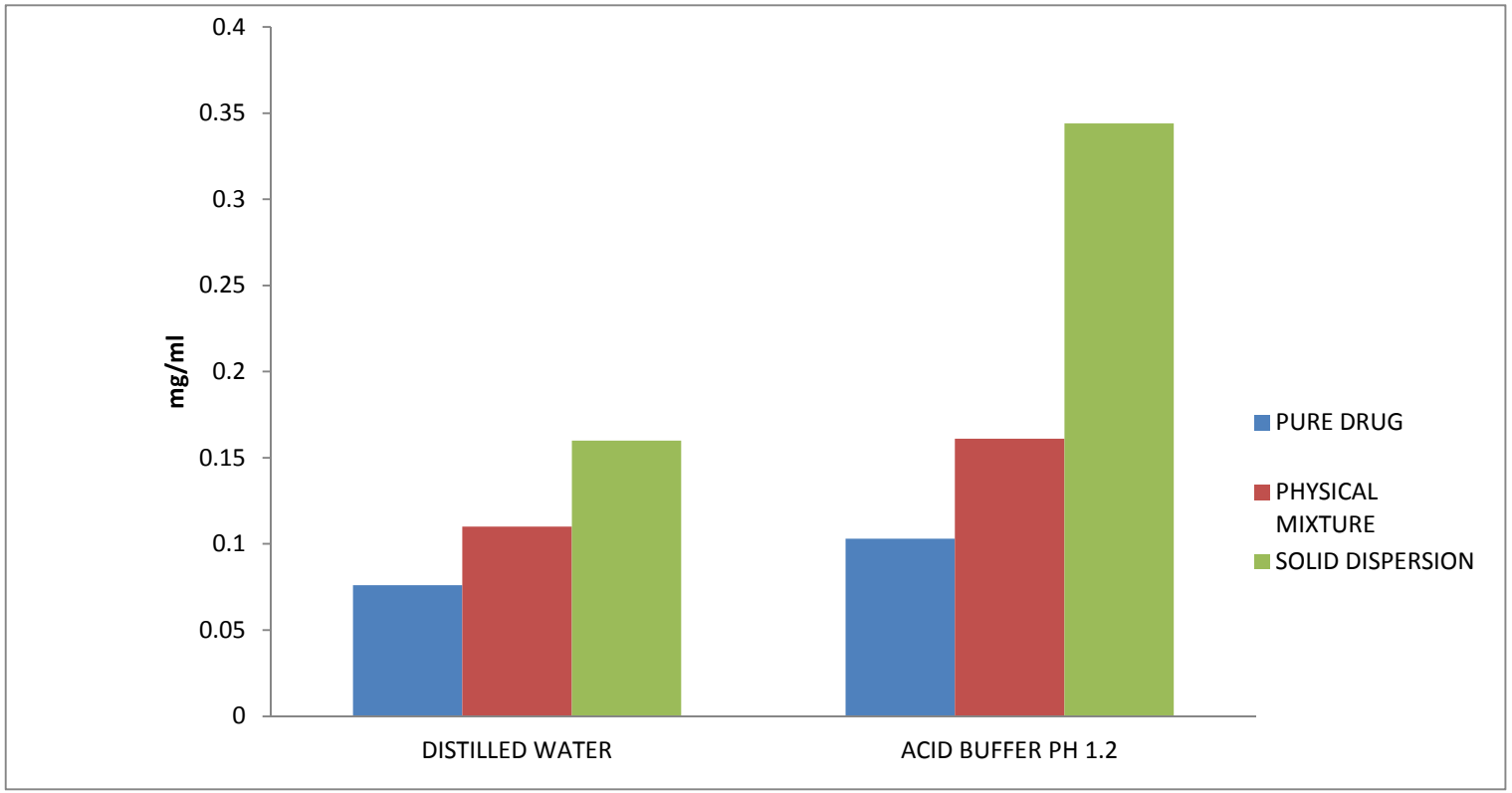


Figure-26 COMPARISON OF SOLUBILITY STUDY OF RACECADOTRIL USING DISTILLED WATER AND ACID BUFFER pH1.2

FT-IR STUDIES

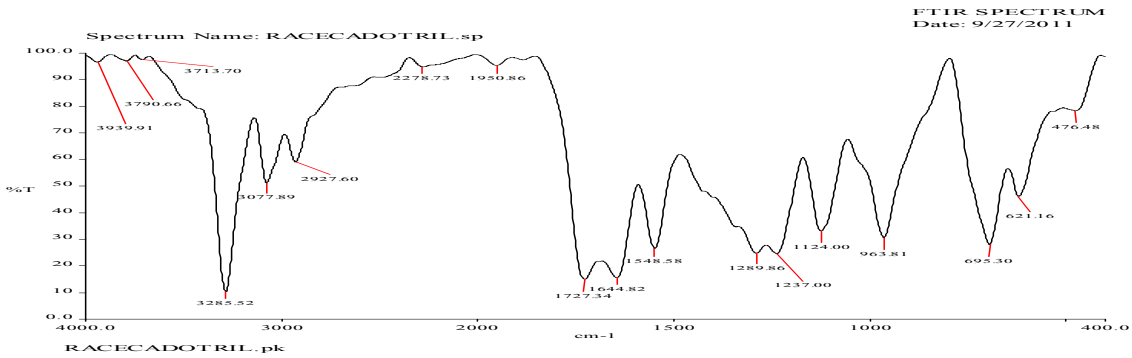


FIG -27 FTIR SPECTRUM OF RACECADOTRIL

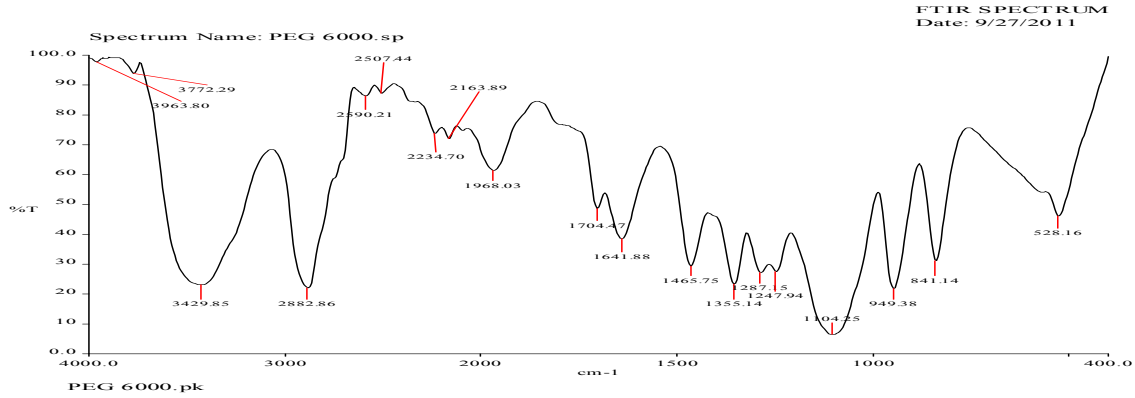


FIG – 28 FTIR SPECTRUM OF PEG 6000

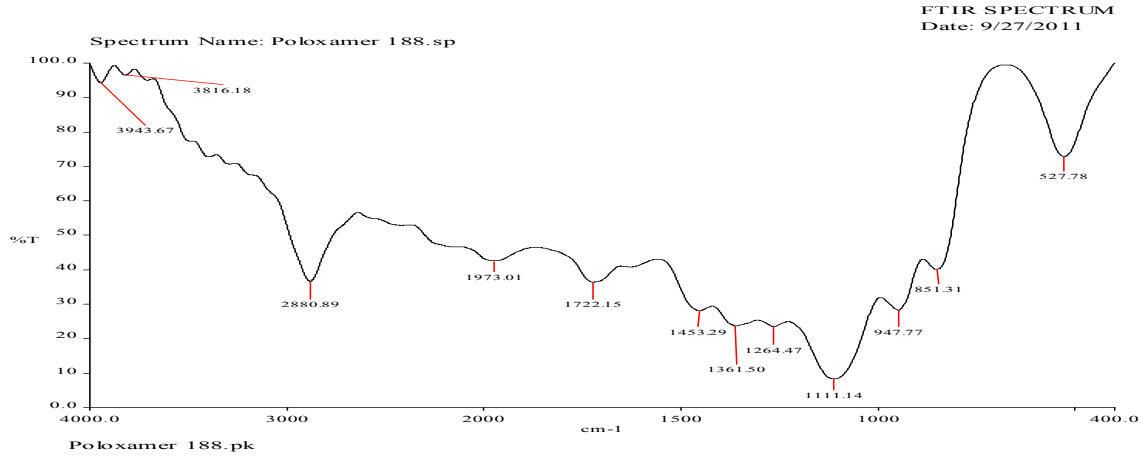


FIG - 29 FTIR SPECTRUM OF POLOXAMER 188

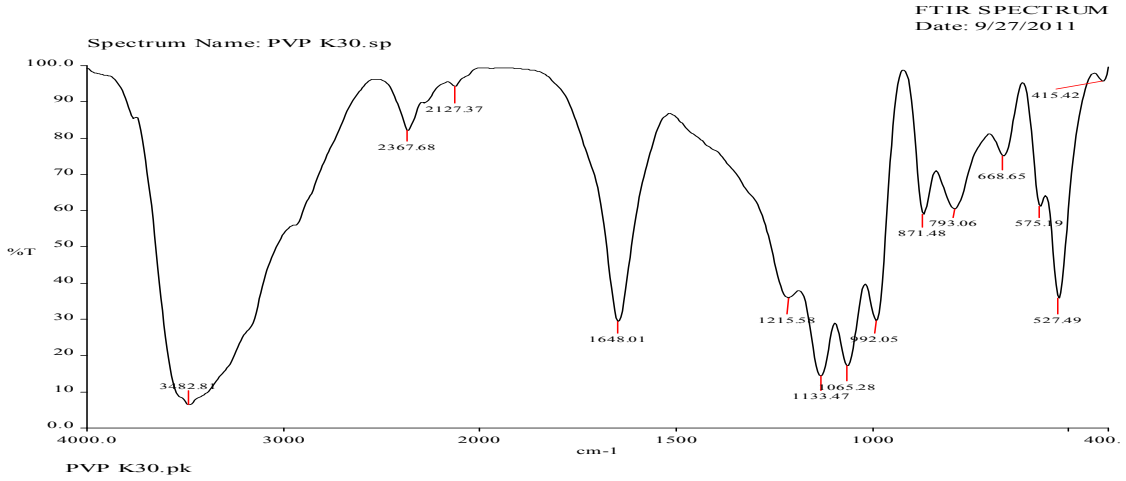


FIG - 30 FTIR SPECTRUM OF PVP K30

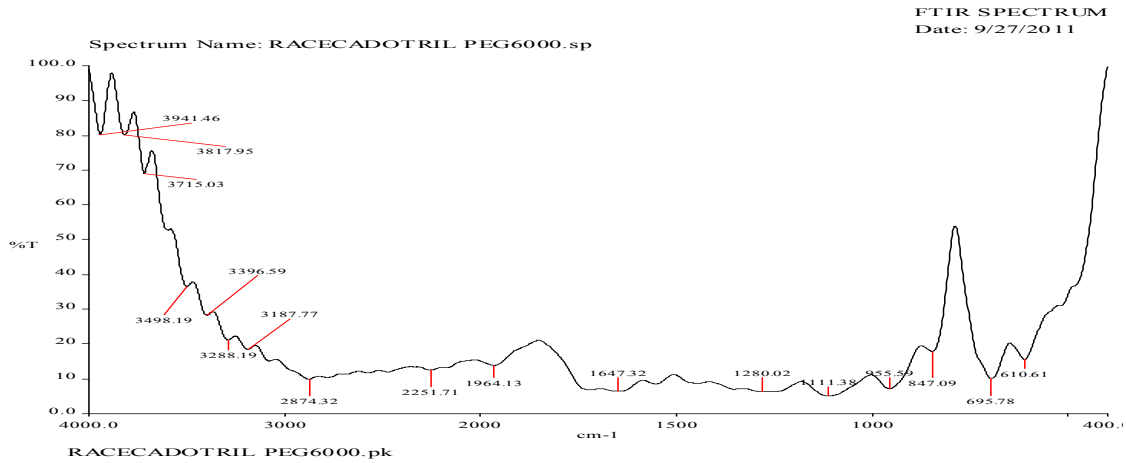


FIG -31 FTIR SPECTRUMS OF RACECADOTRIL+PEG 6000

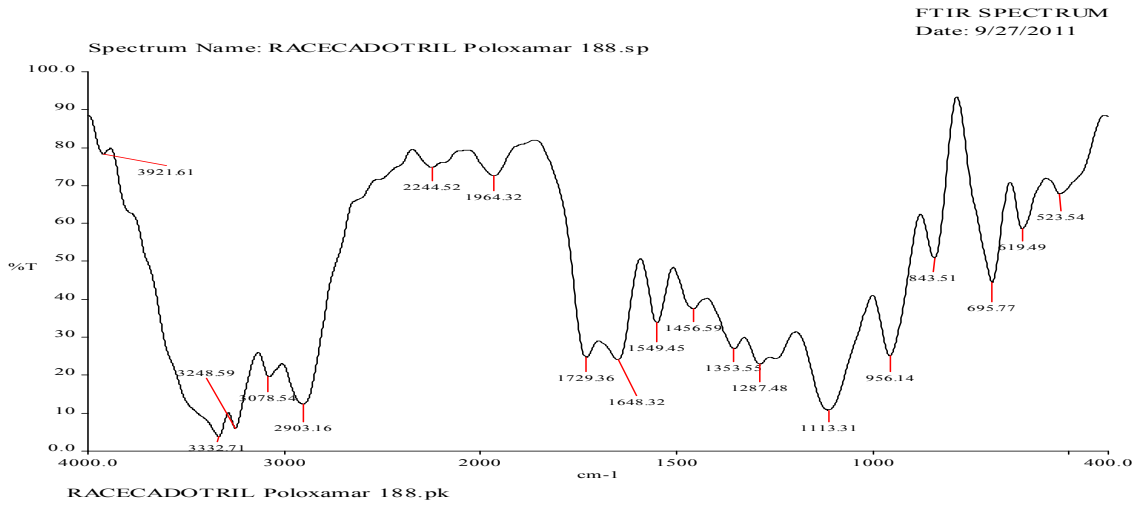


FIG -32 FTIR SPECTRUM OF RACECADOTRIL+POLOXAMER 188

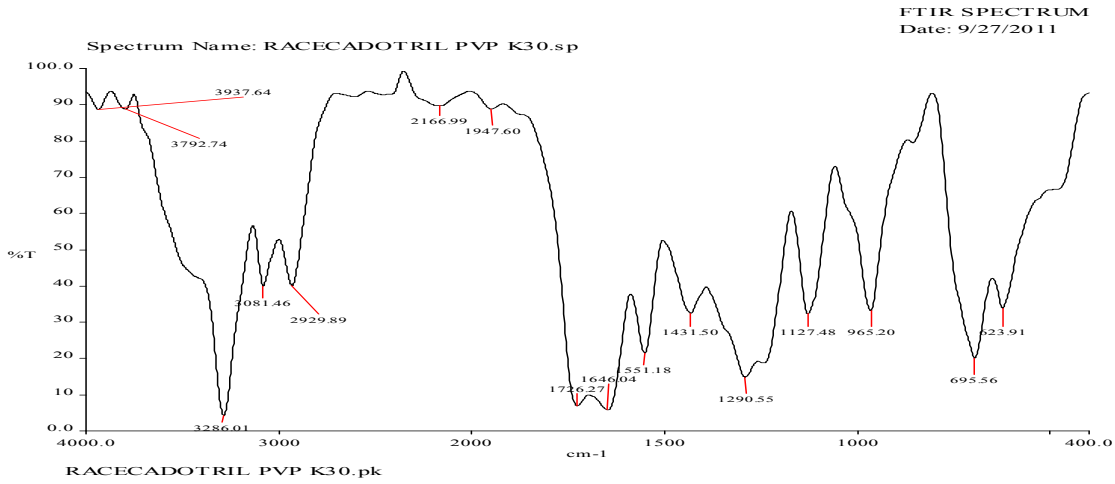


FIG -33 FTIR SPECTRUM OF RACECADOTRIL+PVP K30

DSC STUDIES

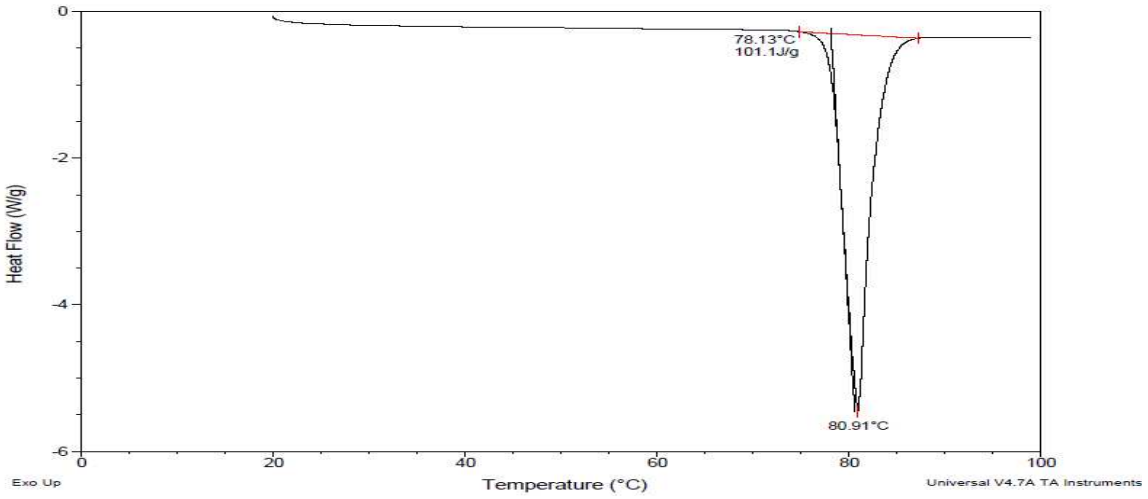


FIG - 34 DSC THERMOGRAM OF RACECADOTRIL

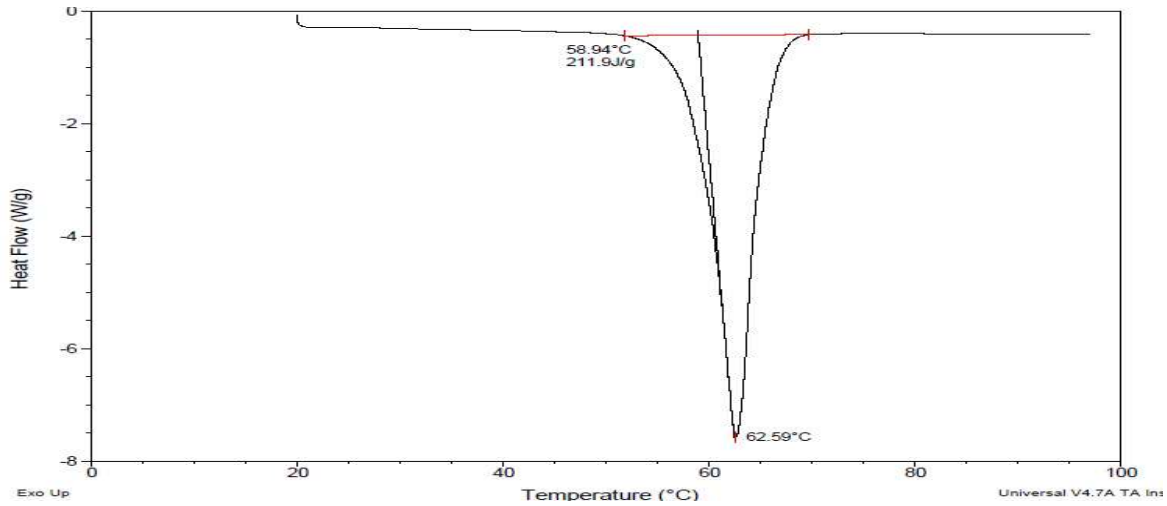


FIG - 35 DSC THERMOGRAM OF PEG6000

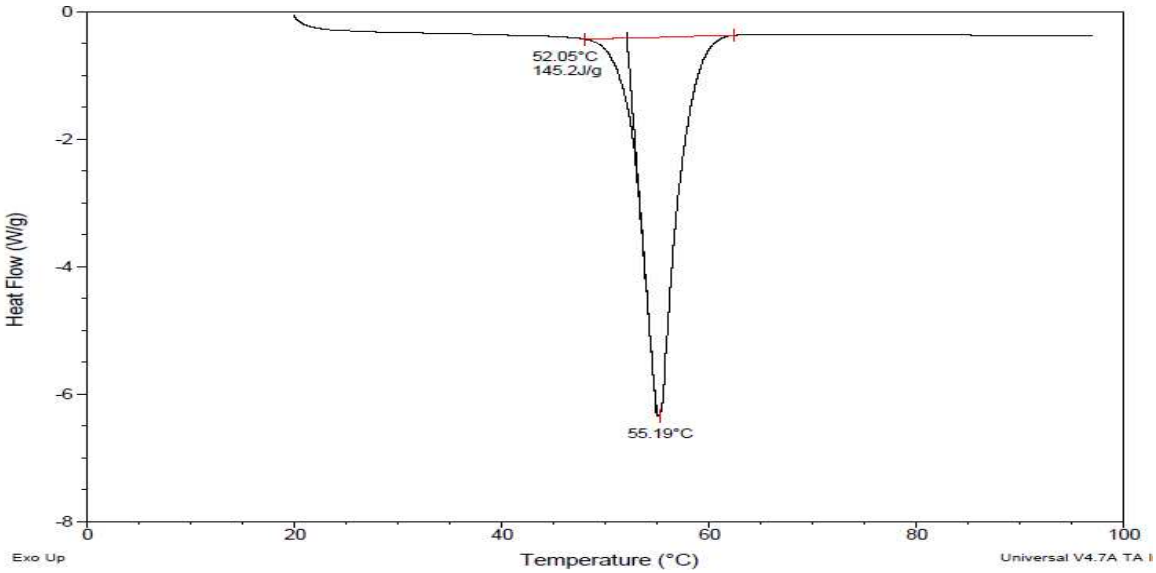


FIG – 36 DSC THERMOGRAM OF POLOXAMER 188

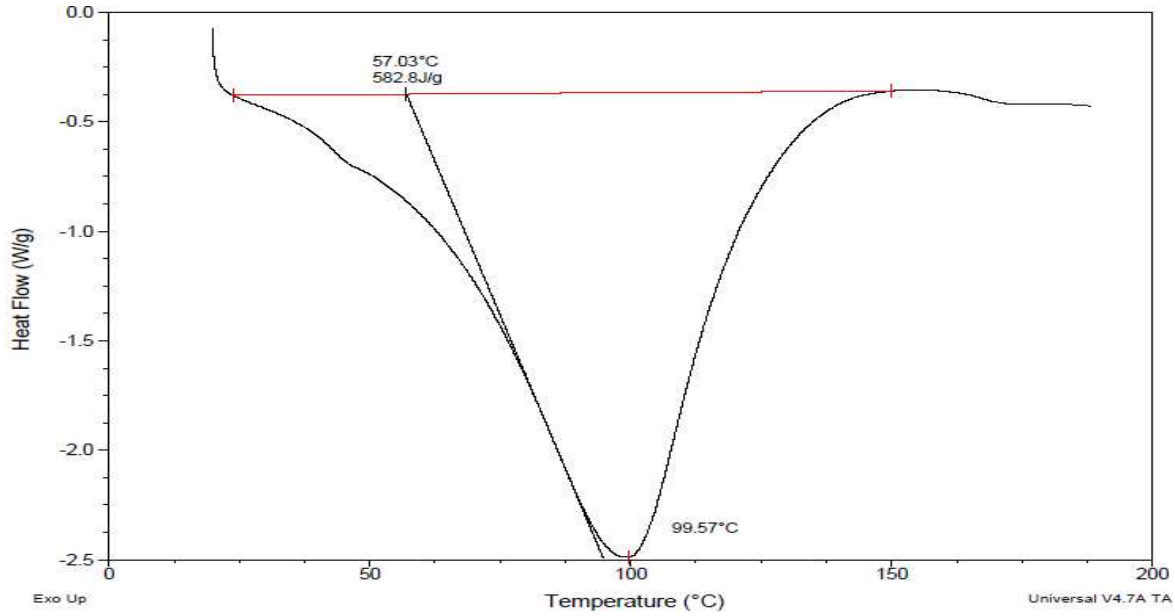


FIG – 37 DSC THERMOGRAM OF PVP 30

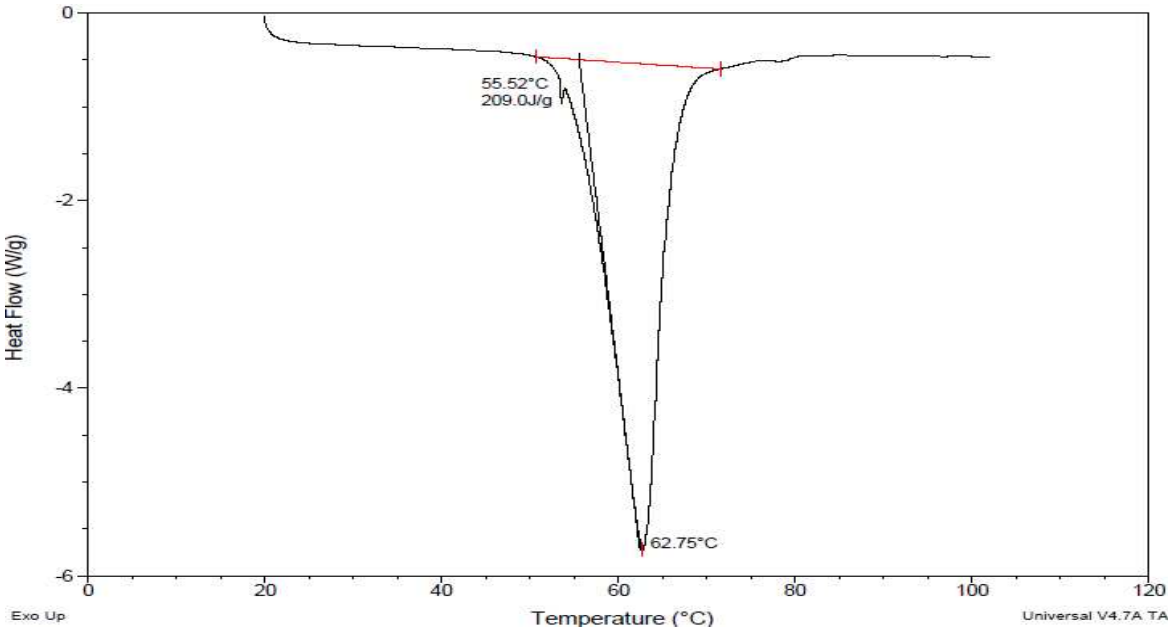


FIG – 38 DSC THERMOGRAM OF DRUG+PEG6000

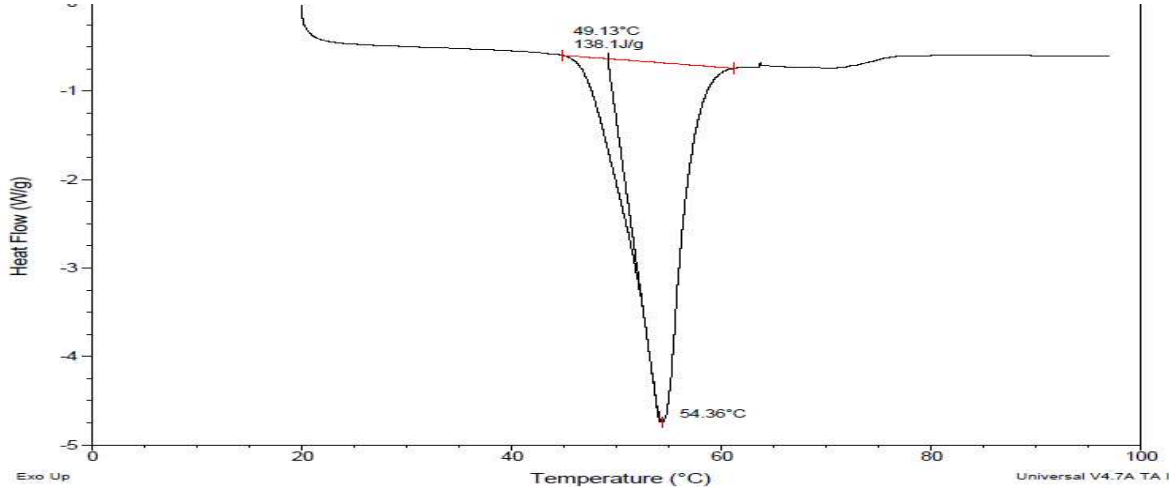


FIG – 39 DSC THERMOGRAM OF DRUG+POLOXAMER 188

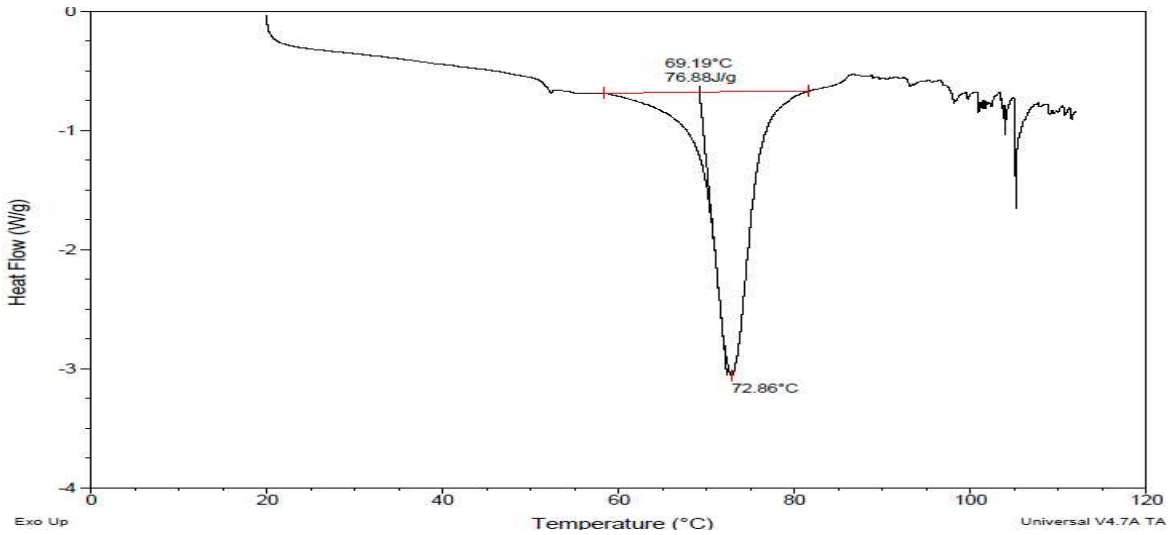


FIG – 40 DSC THERMOGRAM OF DRUG+PVP K30

POWDER X-RAY DIFFRACTION STUDIES

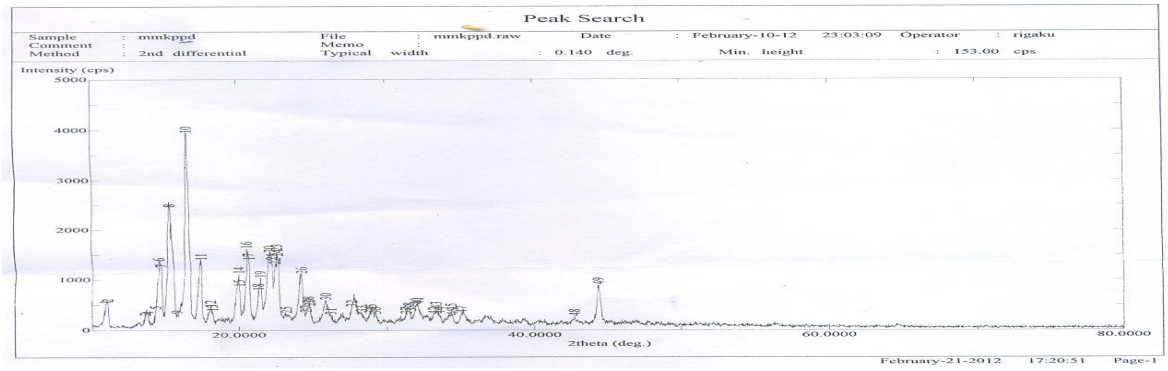


FIG - 41 PURE DRUG (Racecadotril)

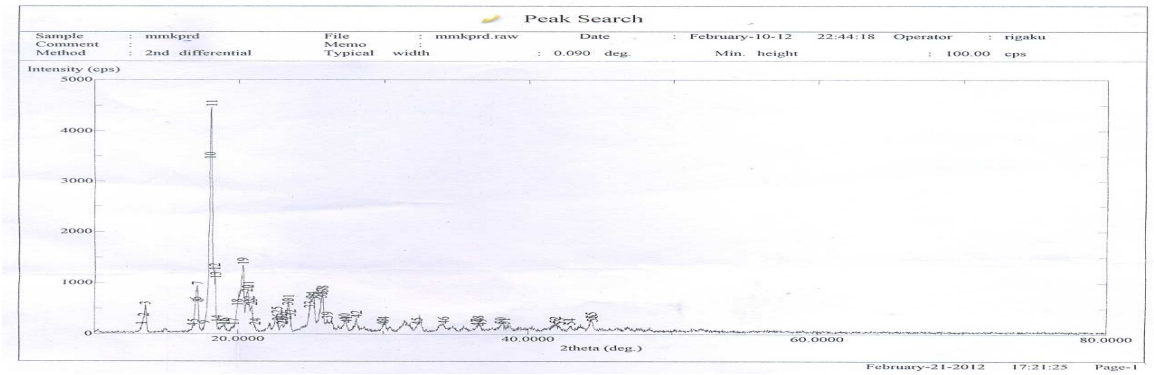


FIG - 42 PHYSICAL MIXTURE (PM 7)

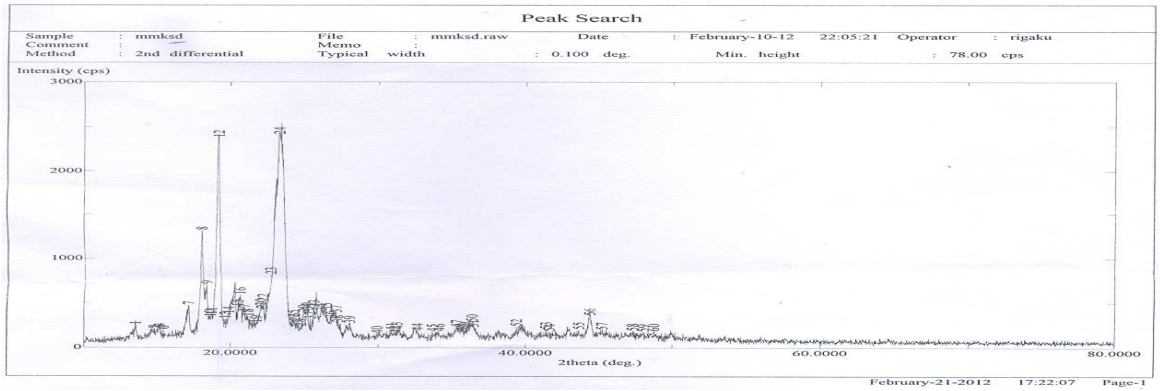


FIG - 43 RACECADOTRIL SOLID DISPERSION (KM7)

CHAPTER- XI

SUMMARY AND CONCLUSION

❖ The purpose of this study was to prepare solid dispersions of Racecadotril to improve the solubility and dissolution rate.

❖ Kneading method, Melting Method, Solvent Evaporation Method and freeze drying methods were employed to prepare solid dispersions.

❖ The formulated solid dispersions were characterized for in vitro release studies in Hydrochloric acid buffer pH1.2, using USP Type I apparatus.

❖ The solid dispersion systems of Racecadotril prepared with the water soluble carriers PEG 6000, Poloxamer 188 and PVP K_{30} show better in vitro release.

❖ The results revealed that the increase in the carrier concentration, decreases the dissolution rate(1:4 ratios). Faster dissolution rate was observed in the order of PVP K30 > Poloxamer 188 > PEG 6000.

❖ The in vitro release studies revealed that the solid dispersion formulations showed a faster drug release compared to the physical mixture and pure drug.

❖ FT-IR studies showed that there is no interaction between the drug Racecadotril and the carriers.

❖ The results of the Powder X-ray diffraction (PXRD) studies proved that crystallinity of the drug Racecadotril was remarkably reduced the best formulation (KM7).

❖ Crystallinity of the drug was reduced in the solid dispersion prepared by using PVP K_{30} in the ratio 1:3 with kneading method.

❖ The solubility studies was observed that the solid dispersion(KM7) have highest solubility compared to pure drug and physical mixture in distilled water and acid buffer pH 1.2.

❖ The DSC thermograms of Racecadotril and of its physical mixtures, the sharp melting point peak of pure racecadotril appeared at 80.9^0C, whereas no such peak was observed in physical mixtures (1:1) prepared with PEG6000, PVP K30 and Poloxamer 188, suggesting that Racecadotril was molecularly dispersed and in an amorphous form.

CONCLUSION:

It is concluded that the kneading, melting, solvent evaporation and freeze drying methods are useful methods for the successful enhancement of solubility of poorly water soluble drug Racecadotril with faster dissolution rate. Further, it may be assumed that the solubility and dissolution rate can be increased due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that solid dispersion of Racecadotri by using the water soluble carrier PVP K_{30} in the ratio 1:3 prepared by kneading method provide best release of drug (72.7% released in 60 mins) among all the formulations, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug Racecadotril.

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REFERANCES

Abu T.M Serajuddin, Hemant N Joshi, Ravindra W Tejwani, **2004.** "Bioavailability enhancement of poorly water soluble drug by solid dispersion in PEG-Polysorbate 80 mixture*". Int. J. Pharm. (269), 251-258.*

Akila Devi.D, Shanmugapandian.P, Jebasingh.D, Sachinandhan Basak, **2011.**"Preparation and evaluation of paracetamol by solid dispersion technique using PEG 4000, 6000 and Urea". *Int. J. Pharm. Sci. 3(1), 103-112.*

Ali Nokhodchi, Hiba Al-Hamidi , Alison A Edwarob ,Mohd A Mohamed, 2010. "To enhance dissolution rate of poorly water soluble drugs, Glucosamine Hcl as a potential carrier in solid dispersion formulation". *Colloids and surfaces B, Biointerfaces .(76) ,170-178.*

Amit R Tapas, Pravin S Kawtikwar, Dinesh M Sakarkar, **2010.**"Spherically agglomerated solid dispersion of valsartan to improve solubility, dissolution rate and micromeritic properties". *Int. J. Drug. Dev.(2),304-313.*

Anjan K Mahapatra, PN. Moorthy, Sudarsan Biswal, Abikesh P.K. Mahapatra, Siba P.Pradhan, 2011. "Dissolution enhancement and physiochemical characterization of valsartan in solid dispersion with ßCD, HP ßCD and PVP K30". *D.T ,39-45*.

Anshu Sharma, C .P. Jain, **2010.** "Preparation and characterization of solid dispersion of valsartan with poloxamer 188". *Der Pharm.Letter 2 (2), 54-63.*

Anshu Sharma, C.P. Jain, 2011. "Solid dispersion – A Promising technique to enhancement of solubility of poorly water soluble drug*". Int. J. Drug. Dev (3) , 149-170.*

Appa Rao B, M.R.Shivalingam, Y.V. Kishore Reddy, Somesekhara Rao, Rajesh.K, Sunitha.N, 2010. "Formulation and evaluation of Aceclofenac solid dispersion for

dissolution rate enhancement using Lactose, Mannitol and urea". *Int. J. Pharm. Sci . Res. 2 (2), 146-150.*

Arun Prasad K , Narayanan N, Rajalaksmi G, 2010. "Preparation and evaluation of solid dispersion of Terbinafine Hcl using PVP K30 and PEG6000". *Int. J. Pharm. Sci. Rev. Res. 3(1), 130-134.*

Aruna Rawat , Surender Verma, Mahima Kaul and Sapna Saini, 2011. Solid dispersion, A strategy for solubility enhancement. *Int. J. Pharm. Tech. 3(2),1062-1099.*

Ashwini kumar G, Ramkumar choudhary, CH Chaitanya, 2011. "Enhancement of solubility and dissolution rate of Irbesartan by solid dispersion technique using crospovidone and microcrystalline cellulose*Asian. J. Pharm. Cli. Ref. 4(2) , 36-40.*

Aulton. M.E, 2002. Pharmaceutics, 2nd Edition. *The science of dosage form design., 21-22.Published by Churchil Livingstone.*

Bindu Madhavi.B , Kusum.B, Krisha Chatanya C.H, Naga Madhu.M, V. Sri Hardha, David Bangi, 2011. "Dissolution enhancement of Efavirenz by solid dispersion and PEGylation technique using PEG6000*". Int. J. Pharm. Inv. 1(1), 29-34.*

Bobe K.R, Subramanya C.R, Sarasija Suresh, Gaikwad D.T, Patil M.D, khade T.S, Garitre B.B, kulkarniV.V, Gaikwade U.T, **2011.** Formulation and evaluation of solid dispersion of atorvastatin with various carriers. *Int. J. Comp. Pharm 1 (2) , 1-6.*

Brahmankar.D.M, Sunil B.Jaiswal, **2009.** "Biopharmaceutics and Pharmacokinetics- A Treatise" *Second Edition, 349-357.Published by Vallabh Prakashan*.

British pharmacopoeia, 2009. *Racecadotril Monograph,1-5. Published by The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA).*

Chauhari P.D, Kulthe V.V, 2008. "Solubility enhancement of Etoricoxib solid dispersions preparation by using gelucire and poloxamer" *.Ind. J. Pharm. Edu. Res.45, 248-258.*

Chemical buyers. *www.chemicalbuyers.com*.

CIMS 2011. Apr-july.113,68-69.

Dehghan M.H.G, Saifee M, Hanwate R.M, 2010. "Comparative dissolution study of glipizide by solid dispersion using PEG6000, Mannitol and PVP K30*". J. Pharm. Sci. Tech. (9),293-297.*

Deshmukh D.B, Gaikwad P.D, Banker V.H, Pawar S.P, 2010. "Dissolution enhancement of Diacerein by solid dispersion technique using $HPMCE_4$, PVP K30". *J. Pharm. Sci. Tech. 2(11) ,734-739.*

Ganesh Chaulang, Kundan Patil, Dhananjay Ghodke, Shagufta Khan, Pramod Yeole, 2008. "Preparation and characterization of solid dispersion tablet of furosemide with Crospovidone". *Res. J. Pharm. Tech. 1(4) , 386-389.*

Ganesh Chaulang, Piyush Papel,Sharwaree Hardikar, Mukul Kelkar,Ashok Bhosale, Sagar Bhise, 2009. Formulation and evaluation of solid dispersion of furosemide in sodium starch glycolate. *Trop. J. Pharm. Res. 8(1), 43-51.*

Gupta Sachin, Srivastav Shruti, Vajpai Meenakshi, **2010.** "Comparative study of solubility enhancement of poorly water soluble drug by solid dispersion and inclusion complex". *J. Pharm. Res. 3(4), 692-696.*

Guy Van Mooter, Ilse Weuts, Dieter Kempen, Annelies De Gorte, Geert Verreck, Jef Peters, Marcus Brewster, **2005.** " Physical stability of the amorphous state of lopramide and two fragment molecules in solid dispersion with the polymers PVP K30 and PVA-VA 64". *Eur. J. pharm. Sci. 25 ,313-320*

.

Harinath N More, Anil J. Shinde, Namdeo R.Jadhav, Kevin C. Garala, 2007. "Solubilization of poorly water soluble drug - A Review". *www.pharmainfo.net. 5(6), 1-24.*

Hoo –Kyun-Choi, Eun-Jun- Kim,Myuang-Kwanchun, Jae Sang Jang , In-Hwa-Lee, Kyes-Re-Lee, 2006. "Preparation of a solid dispersion of felodipine by solvent wetting method using PVP, HPMC and Poloxamer*". Eur. J. Pharm. Biopharm. 64,200-205.*

Indian Pharmacopoeia, *1996*. *Vol-II, A-82-84.Govt.of India. Ministry of Health & Family Welfare. Published by The Controller of publications, Delhi.*

Kothawade S N, Kadam N R, Aragade P D, Baheti D G, 2010. "Formulation and characterization of Telmisartan solid dispersion using PEG4000". *Int. J. Pharm. Tech. Res. 341-347.*

Kshirsagar S J, Bhalekar.M.R, Sable Preetin, Wadekar.S, Madgulkar.A.R, **2009.** "Dissolution improvement of poorly water soluble drug valsartan by dry emulsion and solid dispersion using HPMCE5LV and capmul oil". *J .Pharm. Res. 2(10), 1780-1785.*

Kumar Sandeep, Purokit Suresh, Gupta G D, 2011. "Effect of non ionic surfactant on the solubility and dissolution of simvastatin*". Int. Res. J. Pharm. 2(3), 100-102.*

Laksmana Rao A, Rajeshwari K R R, Sankar G, 2010. "Spectrophotometric methods for the determination of selected drugs in pharmaceutical formulation*". J. Chem. Pharm. Res. 2(1); 280-282.*

Lewis S, Dhirendra K, Udupa N And Atin K, 2009. Solid dispersions, A Review. *Pak. J. Pharm. Sci. 22(2) ,234-246.*

Lt col N Singh, Lt col S Narayan, **2008.** "Racecadotril –A Novel antidiarrheal*". MJAFI . 64, 361-362.*

Lynne S Taylor, Majime Konno, Tetsurou Handa, David E Alonzo, 2008. "Effect of polymer type on the dissolution profile of amorphous solid dispersion containing felodipine". *Eur. J. Pharm. Biopharm. 70, 493-499*

Maria Victoria Margarit, Ines Carmen Rodriguez, Antonio Cerezo, **1994.** "Physical characteristics and dissolution kinetics of solid dispersion of ketoprofen and PEG 6000". *Int. J. Pharm.108 , 101-107.*

Nagasamy venkatesh D, Elango.K , Sankar.S, Vivek G, 2008. "**Solid** dispersion- a unique technique to improve the aqueous solubility of poorly water soluble drug – A Review". *Int. J. Pharm. Res.* 28-37.

Nagasamy venkatesh.D, Sangeeth.S, Samantha.M.K, Suresh.B, Syed Abuthakir K.S, **2008.** "Dissolution enhancement of domperidone using PVP K30 by solid dispersion technique*". Int. J. Pharm. Sci. Nanotech.1(3) ,221-226.*

Patel Bipin, Patel Jayvadan,Thakor Rashmin, Rajput Ganesh, Patel Kalpesh, 2010. "Improvement of solubility of cinnarizine by solid dispersion using PVP K30 and PEG4000*". Int. Res. J. Pharm. 127-131.*

Prasanthi N.L, RamaRao N, Manikiran S.S, 2010. "Studies on dissolution enhancement of lacidipine using PEG, HEC, Dextrin". *Asian J. Pharm. Cli. Res. 3(2),95-97.*

Puratchikody A, Kamalakannan V, Masilamani K, Senthilnathan B, 2010. " Solubility enhancement of poorly water soluble drug by solid dispersion technique- A Review". *J. Pharm. Res. 3(9) ,2314-2321.*

Rajarajeshwari K, Abbulu K, Sudhakar M, 2011. "Development, characterization and solubility study of valsartan using soluplus. *J. Chem. Pharm. Res. 3(1), 180-187.*

Raymond C Rowe, Paul J Sheskey, Sian C.Owen, **2006.** *Hand Book of Pharm. Excip.5th edition, 535-539,545-550,611-616. Published by pharmaceutical press, London.*

Renu Kalyan Wat, Stuti Gupta, Rejendra Kr Songara,Dolly Jain, Sushma Patel, 2001. "Study of enhancement of dissolution rate of carbamazepine by solid dispersion method." *Int. J. Comp. Pharm. 5 (09), 1-4.*

Sasmita Kumari Acharjya and Mathrusri Annapurna, 2010. "Estimation of Racecadotril in pharmaceutical dosage forms by derivative spectrophotometry and liquid chromatographic methods*". J. Pharm. Edu .Res. 1(1), 102-109.*

Shilpi Sinha, Mushir Ali, Sanjula Baboota, Alka Ahuja, Anilkumar, Jacsed Ali , **2010. "**solid dispersion as an approach for bioavailability enhancement of poorly water soluble drug-Ritonavir using gelicire**."** *AAPS. Pharm. Sci. Tech. 11(2), 518-527.*

Sireesha D, Sowjanya M, Shamili I, Lavanya M, Spandana K, Laksmi Y, Narasaish V.L, Kumar A.A, 2011. "Oral bioavailability of poorly water soluble drug by solid dispersion." *The Ind. Pharm.June, 17-20.*

Sivaramakrishna.G, Keshireddy. Angireddy , Jeyachandra Reddy.B, Dinakar P, 2010. "Enhanced dissolution rate of Ibuprofen by solid dispersion using mannitol." *JITPS . 1 (4), 169-175.*

Swain S. K, Niranjan Patra C.H, Sruti J, Bhanoji Rao M.E, 2011. "Design and evaluation of sustain release solid dispersion of verapamil hydrochloride". *Int. J. Pharm. Sci. Nanotech. 3(4), 1252-1262.*

Toshio Ohara, Satoshi Kitamura, Teryuki Kitagawa, Katsuhide Terada, 2005. "Dissolution mechanism of poorly water soluble drug from extended release solid dispersion system with EC & HPMC." *Int. J .Pharm. 302, 95-102.*

Venkates kumar K, Arunkumar. N, Verma P.R.P, Rani C, 2009. "Preparation and *Invitro* characterization of Valsartan solid dispersions using skimmed milk powder as carrier". *Int. J. Pharm. Tech. Res. 1(3) ,431-437.*

Vidyadhara.S, Rameshbabu J, Sasidhar.R.L.C,Ramu.A, Sivaprasad.S,Tejashree M, 2011. "Formulation and evalution of Glimepride solid dispersion and their tablet formulations for enhanced bioavailability". *Int. J. Adv. Pharm. Sci. 2(1), 15-20.*

Yalcin Ozkan, Nazan Doganay, Necati Dikmen, Askin Isimer, 2000. "Enhanced release of Etodolac in PEG". *IL FARMACO. 55, 433-438.*

Yogesh Pore, Vikrant Vyas, Pankaj kumar Sancheti, \Poonam karekar, Mamli shah, 2009. "Physiochemical characterization of solid dispersion system of Tedalafil with Poloxamer 188." *Acta Pharma 59 ,1025-1034.*

Yunzhe, Yang Rui, Zhou Wenliang, 2008. "Nimodipine semi solid capsules containing solid dispersion for improving dissolution using Eudragit E100 and Plasdone S630." *Int. J. Pharm. 359, 144-149.*